

**CARDIAC ARREST IN CHILDREN PRECEDING PICU  
ADMISSION: AETIOLOGY AND OUTCOME IN A  
DEVELOPING COUNTRY**

by

**JOHN ADABIE APPIAH  
APPJOH002**

**SUBMITTED TO THE UNIVERSITY OF CAPE TOWN  
in fulfillment of the requirements for the degree of  
Master of Philosophy (MPhil) in  
CRITICAL CARE PAEDIATRICS**

**Faculty of Health Sciences**

**UNIVERSITY OF CAPE TOWN**

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

DECLARATION

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

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

Signature: Signed by candidate

Date: 13<sup>th</sup> September 2015

## Acknowledgement

I will like to extend my sincere gratitude to Professor Andrew Argent, Pediatric Intensive Care (PICU) Director whose encouragement and guidance contributed to the completion of this work. I appreciate the work done by Dr Shamiel Salie as my supervisor in taking pains to ensure that deadlines are met and also resources needed were made available to me. Associate Professor Brenda Morrow deserves to be acknowledged for her patience and availing herself and time with the data analysis.

I will also like to thank all PICU consultants, senior registrars and all clinicians and nurses who were part of care of patients with cardiac arrest, staff of medical records and neuro-developmental clinic for the role in documentation and data collection.

Special thanks you to my wife Dr Larko Domeryo Owusu and my three children, John, Alan and Eli who sacrificed their comfort during the period of study.

## Table of Contents

DECLARATION .....	ii
Acknowledgement .....	iii
List of Tables .....	vi
LIST OF FIGURES .....	vi
Abbreviations .....	vii
CARDIAC ARREST IN CHILDREN PRECEDING PICU ADMISSION: AETIOLOGY AND OUTCOME IN A DEVELOPING COUNTRY.....	1
Abstract.....	1
CHAPTER ONE .....	2
Introduction .....	2
1.1 Context.....	2
Literature Search Strategy .....	2
Epidemiology of Paediatric Cardiac Arrest – Incidence, aetiology and outcome.....	2
Post cardiac arrest management .....	6
Extra-Corporal Cardio-Pulmonary Resuscitation .....	8
1.2 Ethical consideration.....	8
1.3 Author guidelines of Paediatric Critical Care Medicine .....	9
1.3 Reference .....	9
CHAPTER TWO .....	12
Key words.....	13
Methods.....	13
Study Setting and Population.....	13
Data Collection.....	14
RESULTS.....	16
Location of arrest.....	18
Physiological and laboratory:.....	20
Management of Arrest:.....	21
Post-arrest management: .....	21
Post-arrest organ complication: .....	21
Arrest outcome: .....	21
DISCUSSION.....	23
Incidence .....	23
Aetiology of cardiac arrest.....	23
Duration of cardiopulmonary resuscitation.....	25
Impact of cardiac arrest on neurological and other organ function.....	25

Limitations .....	25
Conclusions .....	26
Recommendations .....	26
Acknowledgement .....	26
Authorship .....	27
References .....	27
APPENDICES .....	32
APPENDIX I: CASE RECORD FORM (CRF) .....	32
APPENDIX II .....	36
APPENDIX III: RXH MPhil Approval.....	36
APPENDIX IV: Instructions for Authors .....	38

List of Tables

**Table 1. Epidemiology characteristics of pediatric cardiac arrest based on ILCOR ..... 3**

**Table 2: Pharmacologic management of cardiac arrest (vasopressor use) ..... 4**

**Table 3. Therapeutic hypothermia and extra-corporal cardiopulmonary resuscitation ..... 7**

**Table 4: Definitions ..... 14**

**Table 5: Patient demographic, anthropometric and circumstances at admission. ....18**

**Table 6: Underlying condition at arrest.....20**

**Table 7: Temperature, electrocardiogram and laboratory characteristics documented at arrest  
..... 21**

**Table 8 Hospital and neurological outcome:.....32**

**Table 9. factors associated with non-survival .....23**

LIST OF FIGURES

**Fig1: Participant enrolment .....17**

## Abbreviations

CPR:	Cardiopulmonary resuscitation
HREC:	Human Research Ethics Committee
IHCA:	In-hospital cardiac arrest
IQR:	Interquartile range
OHCA:	Out-of-Hospital cardiac arrest
OR:	Odds ratio
VF:	Ventricular fibrillation
VT:	Ventricular tachycardia
PEA:	Pulseless electrical activity
PICU:	Pediatric Intensive Care Unit
PIM2:	Pediatric index of mortality 2
POPC:	Pediatric overall performance category score

## CARDIAC ARREST IN CHILDREN PRECEDING PICU ADMISSION: AETIOLOGY AND OUTCOME IN A DEVELOPING COUNTRY

### Abstract

**Objective:** To describe the characteristics and outcomes of children admitted to PICU following cardiac arrest between January 2010 and December 2011.

**Methods:** Retrospective descriptive study of routinely collected data.

**Results:** Of 2501 PICU admissions, 110 (4.4%; 58.7% male) had preceding cardiac arrest, 80.6% of which occurred in hospital. Median (IQR) age was 7.2 (2.5 – 21.6) months; 30.8% had chronic underlying disease. Children presented most commonly with respiratory (n=28, 27.2%), cardiovascular (n= 22, 21.4%), and gastrointestinal disease (n= 20, 19.4%). Twenty-eight (27.2%) arrested while undergoing a procedure.

Cardiopulmonary resuscitation (CPR) was given for median (IQR) 10 (5 – 20) minutes. Thirty-five (34%) patients received no adrenaline, 44 (42.7%) received up to 3 doses of adrenaline, and 24 (23.3%) received more than 3 doses of adrenaline during resuscitation. Duration of CPR and number of adrenaline doses did not significantly influence patient outcome.

Survival to PICU discharge was 63 (61.2%), 57 (55.3%) survived to hospital discharge with half the deaths in PICU occurred within 24 hours of PICU admission. Out of 51 survivors whose neurological status were assessed 32 were normal, 6 had mild disability, 7 had moderate disability and 6 had severe disability.

Standardized mortality ratio (actual/mean predicted) was 0.7. The median (IQR) length of stay in PICU and hospital were 3 (1 – 8) and 27 (9 -52) days respectively.

Pediatric risk of mortality (PIM2) score was the only variable independently associated with mortality on multiple logistic regression (adjusted OR 1.05; 95% CI 1.02 – 1.07;  $p=0.0009$ ).

**Conclusion:** Mortality was lower than predicted in children admitted to PICU following cardiac arrest. Most survivors had normal neurological function on hospital discharge.

## CHAPTER ONE

### Introduction

#### 1.1 Context

Cardiac arrest is the cessation of the functional mechanical activity of the heart determined by absent central pulses, unresponsiveness and apnea.<sup>1</sup> Paediatric cardiac arrest is not an uncommon<sup>2</sup> event and it is associated with death but in certain circumstances it is possible to re-establish cardiac output and survivors may have associated morbidity<sup>3-5</sup>.

Recognition of life threatening illness and appropriate intervention may prevent cardiac arrest. Sometimes early recognition of cardiac arrest will make it possible to resuscitate the patient and return them to full health. There is limited data on factors affecting cardiac arrest in the developing world. Most information used is extrapolated from studies from the developed countries.

Consequences of cardiac arrest in paediatrics include death or neurological sequelae with poor quality of life. It may be useful to identify the group within a cohort of sick children at risk of cardiac arrest where appropriate intervention may prevent cardiac arrest or in cases of arrest could result in favourable outcome.

Even though cardiopulmonary resuscitation following paediatric cardiac arrest is not futile and many children are successfully resuscitated annually many gaps still exist in what is known about post arrest in children. This study is expected to elucidate some factors associated with outcome in the Sub-Saharan region with specific emphasis on the situation in South African context. It is important to know how this centre is doing as compared to the rest of the world in terms of aetiology and outcome.

#### Literature Search Strategy

We searched the following databases up to September 2014: Pubmed (from 1960), Embase/Ovid (from 1974), Google scholar (1960), Medline (1990). We used the Medical Subject Headings (MeSH) terms “arrest”, “heart arrest” OR “cardiac arrest, “epidemiology” “causes”, “management”, “neurological outcome”, “children”, “developing countries” OR ‘Africa’, OR “South America” OR “Asia”. References from identified studies of relevant review studies were searched for further eligible citations. We limited the search to English publications and conducted it in accordance with International Liaison Committee on Resuscitation (ILCOR). We also searched the web to identify online books for citation and reference.

#### Epidemiology of Paediatric Cardiac Arrest – Incidence, aetiology and outcome

There is no consistent data on global pediatric cardiac arrest incidence owing to the different ways in which it has been reported but Young and Seidel<sup>6</sup> reported that in the United States, 16000 children

suffer cardiac arrest annually. Some epidemiological studies based on the Utstein-style reporting as recommended by the International Liaison Committee on Resuscitation (ILCOR) are shown in table 1.

<b>Table 1. Epidemiology characteristics of pediatric cardiac arrest based on ILCOR</b>					
<b>Citation</b>	<b>Population</b>	<b>Sample size</b>	<b>Study type</b>	<b>Entry criteria</b>	<b>Outcome</b>
<sup>3</sup>	Brazil	129 (83 with ROSC)	Prospective study Single center	More than 28 days to 14 years  Cardiac arrest with CPR initiated in the hospital	<ol style="list-style-type: none"> <li>1. Respiratory failure is the most common cause of cardiac arrest</li> <li>2. Preexisting chronic disease were prevalent</li> <li>3. CPR effective</li> <li>4. Survival progressively decreased over time</li> <li>5. One year survival 15%; no demonstrable gross neurological deficit</li> </ol>
<sup>7</sup>	Finland	118 (74 with ROSC)	Single center, retrospective	Less than age 16 years  All patients who received external cardiac compressions or open chest-CPR with sustained ROSC	<ol style="list-style-type: none"> <li>1. Incidence 0.7% of hospital, admission</li> <li>2. Etiology cardiovascular (71%), respiratory (10%)</li> <li>3. 15 of 23 discharge no to mild disability (POPC)</li> </ol>
<sup>8</sup>	Pakistan	106 (58 with ROSC)	Single center, retrospective	One month to 14 years  All IHCA	<ol style="list-style-type: none"> <li>1. Incidence 0.4% of hospital admissions</li> <li>2. Duration of CPR (&gt;20 min) best predictor of mortality</li> </ol>
<sup>9</sup>	Spain	95 (68 with ROSC)	Prospective, multi-center	7 days to 16 years  CA and received CPR out-of-hospital	<ol style="list-style-type: none"> <li>1. Drowning (24), respiratory disease (14) and neurological (13) were top 3 etiology</li> <li>2. CPR effective in 47.3%</li> </ol>

					<p>3. Duration of CPR (&gt;20 min) best predictor of mortality</p> <p>4. One year survival 26.4%; no demonstrable gross neurological deficit</p>
--	--	--	--	--	--

Conclusion: Respiratory diseases and cardiovascular conditions are the most frequent causes of cardiac arrest in the pediatric population.

Questions have been asked about the impact of vasopressor use during resuscitation on patient outcome. Epinephrine has been part of CPR since 1960s when it was recommended in the initial guidelines and continues to be an integral part of advanced life support though there have been very few studies looking at the efficacy and safety of its use following cardiac arrest. The dosage has undergone review but is still part of current ILCOR recommendations, although some studies including those listed in table 2 have raised concerns about its long-term benefit. These show that although it may improve the rate of ROSC, it may decrease chances of survival. Olasveengen et al<sup>10</sup> found that the long term functional outcome of patients without any intravenous medication such as epinephrine and vasopressin was not significantly different from those with epinephrine administration., Jacobs et al<sup>11</sup> showed significant improvement in ROSC. Although the studies were underpowered but reported that epinephrine may have improved the numbers surviving to discharge.

Larabee et al<sup>12</sup> reviewed vasopressor use in pediatric cardiac arrest and concluded that five studies found no differences between high dose epinephrine and low dose epinephrine in ROSC, survival data and neurological outcomes.

<b>Table 2: Pharmacologic management of cardiac arrest (vasopressor use)</b>				
<b>Citation</b>	<b>Population</b>	<b>Sample size</b>	<b>Study type</b>	<b>Outcome</b>
<sup>11</sup>	Australia, 18 years and older  OHCA  Epinephrine vrs Placebo (normal saline)	534	Single center, Double blinded  random controlled trial (RCT)	<p>1. ROSC: significantly improved in Epinephrine arm versus placebo { epinephrine (22 [8.4%] placebo vs. 64 [23.5%] epinephrine; OR 3.4; 95% CI 2.5–5.6)}</p> <p>2. Survival to discharge: No statistical significance between the two groups. {survival to hospital discharge (5 [1.9%] placebo vs. 11 [4%]</p>

				epinephrine; OR 2.2; 95% CI 0.7–6.3)}
13	Japan, 18 years and older  Epinephrine use prehospital arrival and short- and long-term mortality  OHCA	417188	Prospective RCT	<ol style="list-style-type: none"> <li>1. Epinephrine was significantly associated with increased chance of ROSC</li> <li>2. Decreased chance of survival and good functional outcomes 1 month after the event</li> </ol>
10	Norway,  Adults  Intravenous vrs no intravenous medication	851	Prospective RCT	Intravenous access and drug administration had higher rates of short-term survival with no statistically significant improvement in survival to hospital discharge, quality of CPR, or long-term survival.
14	Less than 18 yrs of age  Cardiac arrest requiring chest compressions and  Epinephrine (0.01 mg/kg)	29	Prospective, pilot, matched RCT (with vasopressin rescue)	Provide support for a larger randomized controlled trial of arginine vasopressin therapy
15	Austria, Germany, Switzerland  Adults  Comparing epinephrine Vs vasopressin	1186	Double-blind, prospective, multicenter RCT	<ol style="list-style-type: none"> <li>1. Effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity,</li> <li>2. Vasopressin was superior to epinephrine in patients with asystole.</li> <li>3. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.</li> </ol>
12	Adult		Systemic review	
	Vasopressin vs placebo	4078	3 randomized trials,  One retrospective study  One prospective	<ol style="list-style-type: none"> <li>1. Improvements in return of spontaneous circulation and hospital admission were observed in two trials</li> <li>2. No significant differences were observed in survival to hospital discharge.</li> </ol>

			observational study	
	Vasopressin compared to epinephrine	6440	One meta-analysis, Eight RCTs, Four level three studies and One non-randomized trials One single-group study	1. No differences in failure of ROSC, death before hospital admission death within 24 hours and death prior to hospital discharge

Conclusion: Most of the studies on vasopressor use are in adults over eighteen years and in spite of some adverse effects reported by some studies there is not enough evidence to discontinue vasopressors use during advanced pediatric life support.

### Post cardiac arrest management

There is high mortality following ROSC which is believed to be due to post arrest syndrome, a pathophysiological process occurring in multiple organs resulting after global tissue hypoxia. Management of the post arrest includes monitoring of parameters such as arterial pressure, peripheral oxygen saturation, central venous pressure and urine output and others may allow for the early detection of complications for early intervention. General measures alongside organ specific therapies are targeted at brain injury, myocardial dysfunction, systemic ischemia and persistent precipitating pathology. Post-ROSC patients require general and advanced intensive care monitoring though this has not been validated.

Optimization of oxygen delivery through manipulation of preload, contractility, afterload and blood oxygen content have been used in similar systemic conditions such as sepsis. It is important to reduce hypoxaemic related brain damage.<sup>16</sup> Use of intravenous fluids, inotropes and blood transfusions and early goal directed therapy (EGDT) in sepsis have been recommended in the last ILCOR guidelines but there is little data to support specific goals of blood pressure, plus oxygen delivery following cardiac arrest.<sup>17</sup>

There is increasing evidence <sup>18,19</sup> that therapeutic hypothermia may improve brain function after resuscitation from cardiac arrest in adults. After successful cardio-pulmonary resuscitation and establishment of return of spontaneous circulation, reperfusion of the affected tissues may lead to

complex brain derangements and secondary brain injury. The cascade of events including oxygen depletion, calcium metabolism abnormalities, and re-oxygenation induced chemical injuries that may impair consciousness and outcome<sup>2021</sup>. Distinct regions of the brain (hippocampus, neocortex and cerebellum are more vulnerable to time dependent ischemic injury leading to long term and permanent changes (Kumar et al. 2003).

<b>Citation</b>	<b>Population</b>	<b>Sample size</b>	<b>Intervention</b>	<b>Study type</b>	<b>Outcome</b>
<sup>22</sup>	Taiwan, 2 month to 18 years Cardiac arrest	43	Therapeutic hypothermia (TH)	Retrospective Single center	<ol style="list-style-type: none"> <li>1. Survival rate was significantly higher (P = 0.047) in the therapeutic hypothermia group (11/14, 78.6%)</li> <li>2. No statistical significance in pediatric cerebral functional category score. {Therapeutic hypothermia group (9/11, 81.8%) than in the normothermia group (6/13, 46.1%) with no statistical significance}</li> </ol>
<sup>23</sup>	United States, 1week to 21 years Cardiac arrest	181 cardia arrest (40 TH)	TH	Single center	<ol style="list-style-type: none"> <li>1. Therapeutic cooling was feasible</li> <li>2. No difference in hospital mortality (55.0% therapeutic hypothermia vs. 55.3% standard therapy; p = 1.0)</li> <li>3. Prospective study is urgently needed to determine the efficacy of therapeutic hypothermia in pediatric patients after cardiac arrest.</li> </ol>
<sup>24</sup>	Taiwan Less than 18 years	54	Extra corporeal cardiopulmonary (ECPR)	Retrospective	<ol style="list-style-type: none"> <li>1. Cardiac arrest in patients with isolated cardiac diseases is an appropriate indication for ECPR</li> </ol>

					2. Other reversible causes of cardiac arrest such sepsis, pneumonia and airway obstruction might also be suitable indication for ECPR
--	--	--	--	--	---

Therapeutic hypothermia (TH) is a multifactorial neuro-protective process which includes mitigation of oxygen free radicals, modulation of blood-brain barrier damage, preservation of ATP stores and improvement in post-ischemia microcirculation<sup>252627</sup>.

TH is not without complications, Fink et al (Table 3) showed that TH in paediatric cardiac arrest was feasible and noted that cooling below 32°C was rather detrimental with poor outcome as those in the TH arm received more frequent electrolyte supplementation. It must be noted that the control arm were patients with traumatic brain injury and not cardiac arrest. This study also demonstrated that the risk of infection was no different from control group. Unresolved issues relating to TH include randomized controlled trials to determine ideal temperature, duration of hypothermia and how quickly rewarming take should place.

### Extra-Corporal Cardio-Pulmonary Resuscitation

Extra-corporal cardio-pulmonary resuscitation (ECPR) is another intervention which has been used to augment conventional CPR with increasing favorable outcome even in patients who had longer duration of CPR (>20 min), as reported by Huang et al <sup>24</sup>.

Outcome is significantly better in those who received it earlier.

From the perspective of Africa ECPR is not available for resuscitation following cardiac arrest in children and will not be available for the foreseeable future, and as a result we will not review the limited available data.

### 1.2 Ethical consideration

The research protocol was submitted to the School of Child and Adolescent Health Departmental Research Committee who approved it and was subsequently submitted to the Faculty of Health Sciences Human Research Ethics Committee. Faculty of Health sciences Human Research Ethics Committee of the University of Cape Town approval was obtain, HREC REF: 344/2012, (Appendix I) prior to data collection began. Management of Red Cross War Memorial Children’s Hospital approval was obtained (Appendix II). Informed consent was not obtained because no additional procedure was done.

### 1.3 Author guidelines of Paediatric Critical Care Medicine

The reason for selecting Pediatric Critical Care Medicine journal is because of the specialty it covers and that the subject being researched involves pediatric critical care. Secondly, this journal reaches the pediatric critical care practitioner population which is the expected target audience. Appended (Appendix IV) is the detailed instructions for authors.

### 1.3 Reference

1. Zaritsky A, Nadkarni V, Hazinski MF, et al. Recommended guidelines for uniform reporting of pediatric advanced life support: the Pediatric Utstein Style. A statement for healthcare professionals from a task force of the American Academy of Pediatrics, the American Heart Association, and the European Resuscitation Council. *Resuscitation*. 1995;30(2):95-115.
2. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA J Am Med Assoc*. 2006;295(1):50-57. doi:10.1001/jama.295.1.50.
3. Reis AG, Nadkarni V, Perondi MB, Grisi S, Berg RA. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. *Pediatrics*. 2002;109(2):200-209.
4. Raymond TT, Cunnyngham CB, Thompson MT, Thomas JA, Dalton HJ, Nadkarni VM. Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory inhospital pediatric cardiac arrest: a report from the National Registry of Cardiopulmonary Resuscitation. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc*. 2010;11(3):362-371. doi:10.1097/PCC.0b013e3181c0141b.
5. de Mos N, van Litsenburg RRL, McCrindle B, Bohn DJ, Parshuram CS. Pediatric in-intensive-care-unit cardiac arrest: incidence, survival, and predictive factors. *Crit Care Med*. 2006;34(4):1209-1215. doi:10.1097/01.CCM.0000208440.66756.C2.
6. Young KD, Seidel JS. Pediatric Cardiopulmonary Resuscitation: A Collective Review. *Ann Emerg Med*. 1999;33(2):195-205. doi:10.1016/S0196-0644(99)70394-X.
7. Suominen P, Olkkola KT, Voipio V, Korpela R, Palo R, Räsänen J. Utstein style reporting of in-hospital paediatric cardiopulmonary resuscitation. *Resuscitation*. 2000;45(1):17-25. doi:10.1016/S0300-9572(00)00167-2.
8. Haque A, Rizvi A, Bano S. Outcome of in-hospital pediatric cardiopulmonary arrest from a single center in Pakistan. *Indian J Pediatr*. 2011;78(11):1356-1360. doi:10.1007/s12098-011-0439-4.
9. Lopez-Herce J, Garcia C, Dominguez P, et al. Outcome of Out-of-Hospital Cardiorespiratory Arrest in Children. *Pediatr Emerg Care*. 2005;21(12):807-815.
10. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. *JAMA*. 2009;302(20):2222-2229. doi:10.1001/jama.2009.1729.

11. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation*. 2011;82(9):1138-1143. doi:10.1016/j.resuscitation.2011.06.029.
12. Larabee TM, Liu KY, Campbell JA, Little CM. Vasopressors in cardiac arrest: a systematic review. *Resuscitation*. 2012;83(8):932-939. doi:10.1016/j.resuscitation.2012.02.029.
13. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA*. 2012;307(11):1161-1168. doi:10.1001/jama.2012.294.
14. Carroll TG, Dimas VV, Raymond TT. Vasopressin rescue for in-pediatric intensive care unit cardiopulmonary arrest refractory to initial epinephrine dosing: a prospective feasibility pilot trial. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc*. 2012;13(3):265-272. doi:10.1097/PCC.0b013e31822f1569.
15. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A Comparison of Vasopressin and Epinephrine for Out-of-Hospital Cardiopulmonary Resuscitation. *N Engl J Med*. 2004;350(2):105-113. doi:10.1056/NEJMoa025431.
16. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA J Am Med Assoc*. 2010;303(21):2165-2171. doi:10.1001/jama.2010.707.
17. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-1506. doi:10.1056/NEJMoa1404380.
18. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-556. doi:10.1056/NEJMoa012689.
19. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-563. doi:10.1056/NEJMoa003289.
20. Madl C, Kramer L, Domanovits H, et al. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit Care Med*. 2000;28(3):721-726.
21. Yenari MA, Zhao H, Giffard RG, Sobel RA, Sapolsky RM, Steinberg GK. Gene therapy and hypothermia for stroke treatment. *Ann N Y Acad Sci*. 2003;993:54-68; discussion 79-81.
22. Lin J-J, Hsia S-H, Wang H-S, Chiang M-C, Lin K-L. Therapeutic hypothermia associated with increased survival after resuscitation in children. *Pediatr Neurol*. 2013;48(4):285-290. doi:10.1016/j.pediatrneurol.2012.12.021.
23. Fink EL, Clark RSB, Kochanek PM, Bell MJ, Watson RS. A tertiary care center's experience with therapeutic hypothermia after pediatric cardiac arrest. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc*. 2010;11(1):66-74. doi:10.1097/PCC.0b013e3181c58237.

24. Huang S-C, Wu E-T, Wang C-C, et al. Eleven years of experience with extracorporeal cardiopulmonary resuscitation for paediatric patients with in-hospital cardiac arrest. *Resuscitation*. 2012;83(6):710-714. doi:10.1016/j.resuscitation.2012.01.031.
25. Holzer M, Sterz F, Hypothermia After Cardiac Arrest Study Group. Therapeutic hypothermia after cardiopulmonary resuscitation. *Expert Rev Cardiovasc Ther*. 2003;1(2):317-325. doi:10.1586/14779072.1.2.317.
26. Safar P, Behringer W, Böttiger BW, Sterz F. Cerebral resuscitation potentials for cardiac arrest. *Crit Care Med*. 2002;30(4 Suppl):S140-S144.
27. Kumar R, Krause GS, Yoshida H, Mori K, DeGracia DJ. Dysfunction of the unfolded protein response during global brain ischemia and reperfusion. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab*. 2003;23(4):462-471.

## CHAPTER TWO

Cardiac arrest is a potentially devastating event, which is associated with death or severe neurological complication in survivors. This may occur in previously healthy children as well as in children with underlying diseases or abnormalities. The last fifteen years have seen an improvement in epidemiological data collection of cardiac arrest.(1)(2) whilst the publication of guidelines has contributed to improvement in outcome (3–5). There is, however, still little published data on pediatric cardiac arrest from countries outside the highly industrialized countries.

The true incidence of pediatric cardiac arrest is unknown but for out-of-hospital-cardiac arrest (OHCA), it is estimated to be 9 per 100,000 person years whilst arrest within intensive care units is thought to occur 0.94 times per 100 admissions(6)(7)(8). In children, respiratory and cardiovascular failure are the major causes of cardiac arrest, but cardiac arrhythmias may not be as uncommon as was previously thought (9).

The understanding of factors influencing and the sequence of events leading to cardiac arrest is thought to have contributed to improvement in survival (10). Early recognition of patients at risk for arrest (with intervention and institution of effective cardiopulmonary resuscitation following arrest) will potentially improve survival.(11,12)

Cardiopulmonary resuscitation involving ventilation, chest compression and pharmacological agents are the mainstay of management during cardiac arrest (13). Ongoing monitoring and management following return of spontaneous circulation (ROSC) may also have a significant impact on outcomes. Moreover, measures directed at monitoring and maintaining circulation after return of spontaneous circulation could have significant effect on outcome. Moreover, measures directed at monitoring and maintaining circulation after return of spontaneous circulation could have significant effect on outcome.

Cardiac arrest is defined as the cessation of functional mechanical activity of the heart determined clinically by absent central pulses, unresponsiveness and apnea(14–16). Absence of blood flow leads to non-perfusion of vital organs including the brain, kidneys and the heart muscle (17,18). Prolonged ischemia ultimately leads to cell death and abnormal function of these organs.

Though the process of cardiac arrest and resuscitation is a continuum, it may be seen to consist of four phases and usually begins with pre-arrest, no-flow, low flow and return of spontaneous circulation(19)(20). The pre-arrest phase may be associated with respiratory failure or shock states, and it is associated with asphyxia and/or ischemia resulting in inadequate delivery of substrate for cellular metabolism. This phase, if untreated, leads to established cardiac arrest

involving no-flow, the cessation of mechanical activity of the heart and absent pulses. Low-flow phase ensues when intervention is instituted. The main goal of intervention at this stage is to optimize cerebral, coronary and other vital organ perfusion. Providing effective uninterrupted chest compression is key to a successful outcome at this stage.(21) Abnormalities in oxygenation and ventilation are also common during the initial hours after pediatric cardiac arrest.(22) It makes clinical sense to optimize oxygenation and hemodynamic stability (23)(24) with ventilator support, fluids and inotropic support as required, to ensure improved survival of cardiac arrest patients.(25)

Advances in therapeutic hypothermia(TH) have allowed its use in the management of post anoxic brain injury (26) in adults following cardiac arrest from ventricular fibrillation. Therapeutic hypothermia has been shown to be the one of the interventions that reduces mortality in cardiac arrest.(26,27) TH has also been used in newborns with hypoxic ischemic encephalopathy, which has similar mechanisms of injury as post cardiac arrest syndrome in most age groups but probably different in adults: mainly ischemia, global hypoxia, reperfusion injury, with generation of highly toxic oxygen radicals and excitotoxic molecules coupled with cerebral auto-regulation abnormalities.(28–30). Current evidence for TH use in children does not refute or support its use and more randomized controlled studies are needed to evaluate its use since no differences in hypothermia-related adverse events were found between groups.(31) In addition TH requires significant resource allocation and its use should be based on strong evidence of its utility.

Forty to fifty five percent of out-of-hospital-cardiac-arrest in children occur in infants compared with other age categories (7,32–34). The main objectives of this study are to describe the characteristics and outcomes of PICU patients admitted following a cardiac arrest, and review factors associated with outcome, based on the Utstein-Style reporting of cardiac arrest(35)

#### Key words

Pediatric, cardiac arrest, cardiopulmonary resuscitation (CPR), pediatric overall performance category score (POPC), pulseless electrical activity (PEA), Ventricular tachycardia (VT) pediatric intensive care unit (PICU), in-hospital cardiac arrest (IHCA), out-of-hospital cardiac arrest (OHCA)

#### Methods

##### Study Setting and Population

This retrospective study was conducted at the Pediatric Intensive Care Unit (PICU) of the Red Cross War Memorial Children's Hospital in Cape Town, South Africa. This children's hospital is a university teaching hospital with 290 pediatric beds. The multi-disciplinary PICU consists of twenty two

functional beds and accepts patients aged from 0 to 13 years from general pediatric wards, the Emergency and Trauma Department, surgical wards and operating theatres within the hospital and also serves as a referral center for patients in the Western Cape Province of South Africa.

Although there is no dedicated response team in the event of cardiac arrest or potential collapse within the hospital, an intercom system is used to alert doctors (lead by the most senior being a consultant, paediatric registrars or anaesthesia registrars) to the site of the event assisted by nurses on the ward. In cases of out-of-hospital cardiac arrests the patient may be resuscitated a by-bystander or if available by a trained emergency medical technician. There is no clear protocolised guide to termination of CPR, this decision is taken by the resuscitation team when they think treatment is futile after 20 to 30 minutes.

The study population consisted of all children less than 14 years who were admitted to the PICU following a cardiac arrest between 1<sup>st</sup> January 2010 and 31<sup>st</sup> December 2011. The patients were identified through review of the PICU electronic database; the records were then extracted from the patient hospital record and entered into case record form. The information was then entered into a 2010 Microsoft excel database.

#### Data Collection

The questionnaire (Appendix II) was designed to describe patient characteristics, severity of illness, treatment, and outcome characteristics of the cardiac arrest (35). We defined a case as any child who was admitted to the PICU following a documented cardiac arrest outside of the PICU. Records were reviewed to determine the likely cause of the arrest. Only confirmed cases of cardiac arrest who received cardiopulmonary resuscitation (CPR) (36) were included in the study. In patients who had multiple arrests, the data from the first arrest was used.

Patient demographics (age, weight and sex), pediatric index of mortality 2 (PIM2) score, (37) event location (in-hospital or out of hospital), circumstances (expected, deterioration, unexpected or during a procedure) and underlying or primary condition were recorded. Other variables are defined in table 4.

**Table 4: Definitions**

Case definition	Patient who had return of spontaneous circulation following CPR for cardiac arrest
Cardiac arrest	Cessation of functional mechanical activity of the heart with central absent pulses, unresponsive and apnea (14,15)
Apnea	Cessation of breathing of more than 20 seconds (15,38)
Primary diagnosis	The main condition treated or the most clinically severe or life threatening condition that was deemed likely to have led to cardiac arrest
Bradycardia	Heart rate less than 80 beats per minute in the newborn to 2 years of age or less than 60 beats per minute in patients older than
Tachycardia	Heart rate more than 160 beats per minute in the newborn to 2 years of age or more than twice normal for age
Hyperthermia	Documented axillary temperature more than 38.5°C
Hypothermia	Documented axillary temperature less than 35.5°C

Shock	A combination of any of the following: abnormal mental status, weak thready pulses, prolonged capillary refill time and cold extremities (39) and low blood pressure
Acute kidney injury	Documented urine output and creatinine level post arrest episode then with specific p-rifle criteria to categorize the injury(40)

Post-arrest biochemical data (blood sugar, pH, sodium, potassium, chloride, calcium, creatinine and lactate), post arrest treatment (41) (inotrope support, mechanical ventilation, fluid and electrolyte management and treatment of primary cause), level of consciousness at PICU discharge (alert, verbal, pain and unresponsive)(42), event outcome on PICU (survive to discharge from PICU, PICU mortality, ward survival and ward mortality), length of stay in the PICU and length of hospital stay were also recorded. As a general policy the management of post arrest syndrome(25) and its complications are based on targeting normal temperature or mild hypothermia, blood glucose up to 8-10mmol/l (43), ventilation support and early goal-directed hemodynamic stabilization. The ventilation strategy was to achieve normal oxygenation with the use of minimal supplemental oxygen and ventilation using lung protective strategies such as tidal volume target of 6-8 ml/kg.(20, 38)

Neuro-cognitive assessment was done during the course of the patients' admission on the ward by the neuro-developmental team, occupational therapist or ward doctors assessment using Pediatric Overall performance Category Score.(45)

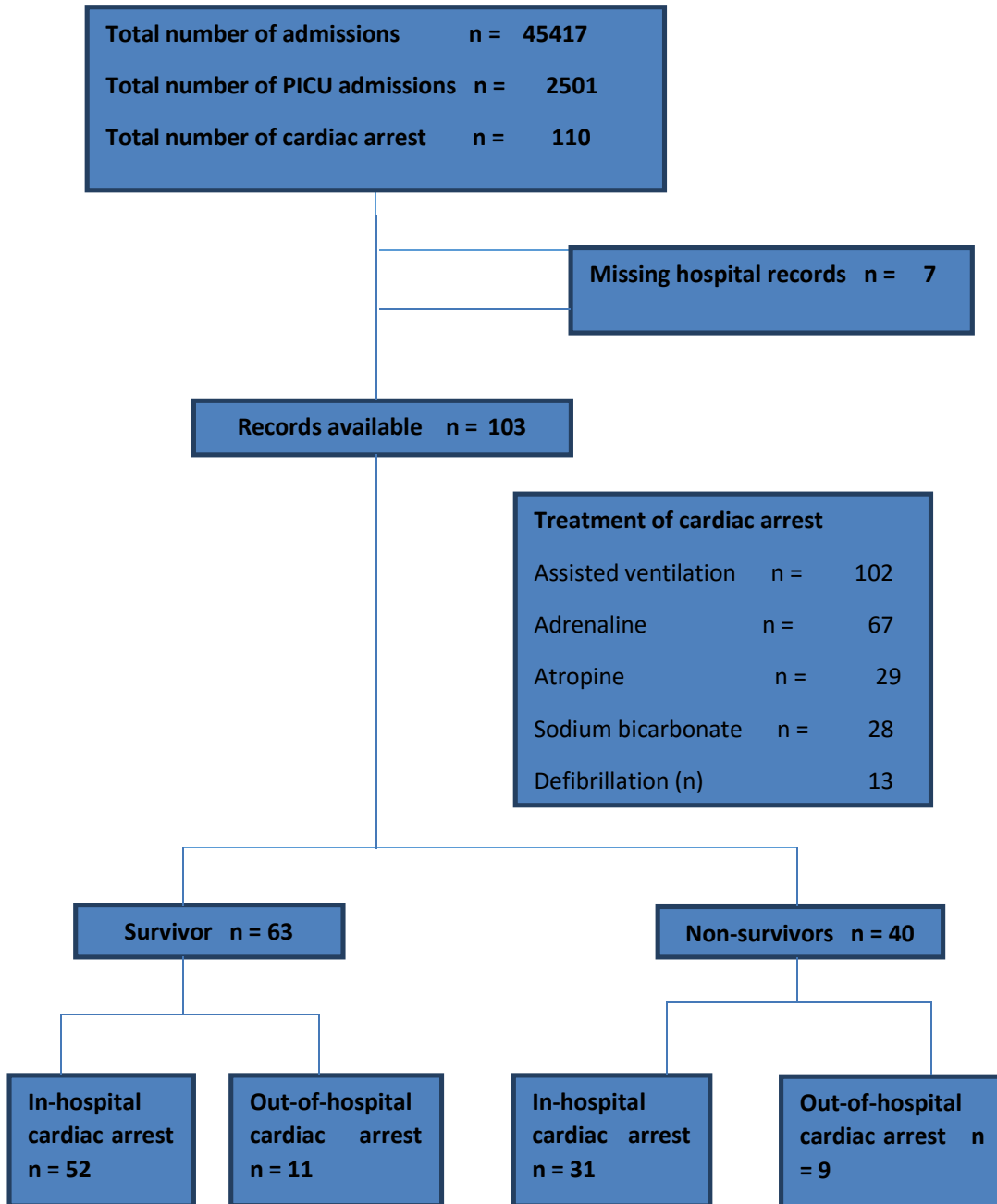
Faculty of Health sciences Human Research Ethics Committee of the University of Cape Town approval was obtained prior to data collection. Informed consent was waived owing to the retrospective nature of the study.

Data collected by the principal investigator was entered into a case record form modified for in-hospital cardiac arrest from the Utstein-Style guidelines (35).

Data were captured in Epi Info™ 7.0.9.7 software and exported onto 2010 Microsoft Excel software. Statistica version 11 (Statsoft Inc. USA) was used to analyze the data. The Shapiro-Wilk test was applied to examine whether the numerical variables data followed a normal distribution so that the appropriate parametric or non-parametric test could be applied. Numerical variables were presented as medians and inter-quartile ranges. Mann-Whitney-U test was used as test of significance of survivors and non-survivors of cardiac arrest event with significant p-value of <0.05. For categorical variables, the test for associations included Pearson's chi-squared test with 95% confidence intervals. A stepwise logistic model was used to identify variables independently associated with outcome. Factors significantly associated with outcome on univariate analysis ( $p < 0.05$ ) were entered into a backward logistic regression analysis model, adjusted for patient age, gender and pediatric risk of mortality (PIM 2) score.

## RESULTS

A total of 45417 patients were admitted to the hospital over the period of the study, 2501(5.5%) of them required PICU admission. One hundred and ten (Fig. 1) patients who had cardiac arrest preceding PICU were identified during the study period, representing a hospital incidence of 2.2 per 1000 hospital admissions.



**Figure 1: Participant enrolment flow chart based pediatric Utstein style reporting template**  
*\*IHCA, in-hospital-cardiac arrest; \*\*OHCA, out-of-hospital cardiac arrest*

The patient characteristics are shown in Table 1. The median risk of mortality as assessed using PIM2 was 0.535; IQR0.284-0.845. Most of the patients, 71 (68.9%), were previously well and 32 (30.—1.1%) had underlying chronic disease.

**Table 5: Patient demographic, anthropometric and circumstances at admission.**

<b>Characteristic</b>	<b>N (%)</b>			
<b>Gender (male: female)</b>	60:43 (58.7:41.3)			
<b>Age (months)</b>	7.2 (2.5 – 21.6)			
<b>Age category (%)</b>				
- <1 month	12 (11.5)			
- 1 – 12 month	52 (50.0)			
- >12 - 36 month	22 (21.2)			
- >36 – 72 months	10 (9.6)			
- >72 months	7 (6.7)			
<b>Weight (kg) (IQR)</b>	5.8 (3.7 – 10.0)			
<b>PIM2 score</b>	0.535 (0.284 – 0.845)			
<b>Reason for admission</b>				
Neurological	9 (8.7%)			
Respiratory	30 (29.1%)			
Cardiovascular	22 (21.4%)			
Gastrointestinal	22 (21.4%)			
Trauma	3 (2.9)			
Other	17 (16.5%)			

<b>Arrest event Outcome</b>	<b>N (%)</b>	<b>Survivors (%)</b>	<b>N</b>	<b>Non-survivors (%)</b>	<b>N</b>
<b>OHCA</b>	<b>20 (19.4)</b>	<b>11 (55)</b>		<b>9 (45)</b>	
Home	10	6		4	
Public	10	5		5	
<b>IHCA</b>	<b>83 (80.6)</b>	<b>52 (62.7)</b>		<b>31 (37.3)</b>	
Emergency	18 (21.7)	13		5	
Wards	41 (49.4)	24		17	
Theatre	8 (9.6)	4		4	
Other	16 (19.3)	11		5	

Data are presented as median (interquartile range) or n (percentage).

#### Location of arrest.

There were 83 (80.6%) patients who had in-hospital cardiac arrest (IHCA) and 20 (19.4%) who had OHCA (Tab 5). Fifty two (62.7%) of the IHCA patients survived to hospital discharge while 11 patients (55.0%) with OHCA survived to hospital discharge ( $p = 0.7$ ). Sixteen (19.3%) of the IHCA were grouped as others (5 in other hospital location, 6 during inter-facility transport whilst 2 occurred during cardiac catheterization and 1 undocumented). Fifteen (18.1%) of IHCA occurred in facilities outside the index hospital and 6 (7.2%) during inter-hospital transfer in the ambulance.

Table 6 shows the primary underlying condition for which the subjects were treated. Thirty seven (35.9%) cardiac arrests were unexpected, 29 (28.2%) resulted from progressive deterioration in patients with an existing medical condition, 28 (27.2%) arrested while undergoing a procedure, 4 patients (3.9%) arrests were expected and 9 (8.7%) the underlying conditions were not documented. Of the 28 who

arrested during a procedure 24 (85.7%) occurred while undergoing endotracheal intubation and anesthesia, 2 occurred intra-operatively, 1 occurred during cardiac catheterization and the other one during central venous line insertion. Sixteen (66%) of the 24 that occurred during endotracheal intubation and anesthesia occurred in the medical emergency department, other hospitals and the wards whilst the other third occurred in theatre. Only 2 (12.5%) out of 16 patients who arrested whilst undergoing a procedure had senior medical staff supervision during the procedure. Four out of five patients who were in shock were on inotropes prior to arresting during endotracheal intubation. Only in one of the eight who arrested in the theatre occurred during endotracheal intubation.

**Table 6: Underlying condition at arrest**

<b>RESPIRATORY</b>	<b>30 (29.1%)</b>	<b>GASTRO-INTESTINAL</b>	<b>22 (22.4%)</b>
Acute lower respiratory tract infection	21	- Acute diarrhoeal disease	14
- Tuberculosis	1	- Necrotizing enterocolitis	3
- Foreign body aspiration	2	- Intestinal perforation	2
- Aspiration	4	- Bowel obstruction	1
- Tension pneumothorax	1	- Gastric haemorrhage	1
- Pulmonary haemorrhage	1	- Protein energy malnutrition	1
<b>CARDIOVASCULAR</b>	<b>22 (22.4%)</b>	<b>OTHERS</b>	<b>17 (16.5%)</b>
Congenital Heart Disease	16	- Drowning	5
Dilated cardiomyopathy and myocarditis	6	- Sepsis	5
		- Hematologic/oncologic	3
		- Poisoning/drug overdose	2
		- Disseminated tuberculosis	1
<b>NEUROLOGICAL</b>	<b>9 (8.7%)</b>	- Burns	1
- Tumour	3		
- Hydrocephalus	1	<b>TRAUMA</b>	<b>3 (2.90%)</b>
- Meningitis	1	- Abdominal	1
- Subdural haemorrhage	1	- Non-accidental injury	1
- Cerebral abscess	1	- Pedestrian motor-vehicle-accident	1
- Encephalitis	1		
- Tuberculous meningitis	1		

**Physiological and laboratory:**

Nineteen (18.4%) patients had a documented cardiac rhythm at arrest, 4 had pulseless electrical activity, 10 asystole and 5 had ventricular tachycardia or fibrillation (Tab 7). Seventeen had their temperature at arrest documented with 14 being hypothermic, 1 normothermic while 2 had hyperthermia. Median blood sugar was 6.3 mmol/l (IQR 4.3-13.5 mmol/l) at the time of cardiac arrest. Median pH following ROSC was 7.16 (IQR 6.99 -7.30). Median lactate level after arrest episode was 5.35 (IQR 2.35-11.55).

**Table 7: Temperature, electrocardiogram and laboratory characteristics documented at arrest**

Temperature at arrest	
- Hypothermic	14
- Normothermic	1
- Hyperthermic	2
- Missing data	86
First documented rhythm	
- PEA	4
- Asystole	10
- VT/VF	5
- Missing	84
Blood sugar (mmol/l) at arrest	6.3(4.3 – 13.5)
First pH at PICU admission (mmol/l)	7.16 (6.99 – 7.3)
Sodium (mmol/l)	138.0 (134.0 – 142.0)
Potassium (mmol/l)	4.1 (3.6 – 5.1)
Chloride (mmol/l)	106.0 (101.0 – 110.0)
Ionized calcium (mmol/l)	1.26 (1.12 – 1.60)
Creatinine (µmol/l)	60.0 (36.5- 88.0)
Lactate (mmol/l)	5.35 (2.35 – 11.55)

#### Management of Arrest:

The median duration of resuscitation was 10 minutes (IQR 5 – 20). Thirty-five (34%) did not receive any adrenaline during the resuscitation, 44 (42.7%) received up to 3 doses of adrenaline, 24 (23.3%) received more than 3 doses of adrenaline. Thirteen (12.7 %) of the patients received at least one defibrillation. One (1%) patient was cardioverted for supra-ventricular tachycardia following CPR. The duration of CPR, number of adrenaline doses or other pharmacological treatment had no statistically significant effect outcome of arrest.

#### Post-arrest management:

Ninety eight (99%) received mechanical ventilation after return of spontaneous circulation. One patient received non-invasive continuous positive airway pressure. The median duration of mechanical ventilation was 2 days (IQR 0-5). Seventy four (71.82%) received inotropes during their PICU admission.

#### Post-arrest organ complication:

Circulatory failure was the most common complication following cardiac arrest with 71 (68.9%) being shocked following the arrest. Twenty five (24.3%) had neurological and 25 (24.3%) had acute kidney injury. Table 4 demonstrate laboratory values, they were mostly normal with the exception of pH, lactate and serum creatinine.

#### Arrest outcome:

Sixty three (61.2 %) of the study population survived to PICU discharge (Tab 8). Twenty of those patients who died occurred within 24 hours of arrest. Fifty seven (55.3%) survived to hospital discharge. Forty nine were discharged from the ward, 8 were transferred to other hospitals, 4 died on the ward (2

of the deaths were unrelated to the cardiac arrest and the other 2 were undocumented). Fifty two (62.7%) of IHCA and 11(55%) of OHCA survived to PICU discharge. Forty nine (47.6%) of those patients who were discharged from hospital were assessed at 3 to 6 month on follow-up visit neurologically and developmentally. The median length of stay in PICU was 3 (IQR 1 – 8) days and the median hospital stay was 27 days (IQR 9 -52).

Neurological assessment by level of consciousness, 54 of the 63 survivors were discharged from PICU alert, 1 was responsive to voice, 4 to pain and 1 was unresponsive. Characteristics of Pediatric Overall Performance (POPS) Score is shown in table 5.

<b>Table 8 Hospital and neurological outcome:</b>	
Up to six month follow-up neurological assessment (POPS) results based on 51 out of the 57 patients discharged home	
<b>Outcome</b>	<b>N (median)</b>
PICU length of stay(days)	3.0 (1.0 – 8.0)
PICU Survival	63(61.2%)
Hospital length of stay(days)	27 (9 – 52)
<b>Ward outcome</b>	
Discharge from hospital	57
Died	4
Missing	2
Death on ward (n=4)	4
- Cardiac arrest related	0
- Unrelated to cardiac arrest	2
- Missing	2
<b>POPS assessed at ward discharge (n)</b>	
Normal	<b>32 (62.7%)</b>
Mild disability	<b>6 (11.8%)</b>
Moderate disability	<b>7 (13.7%)</b>
Severe disability	<b>6 (11.8%)</b>
Coma/vegetative state	<b>0</b>

<b>Table 9. factors associated with non-survival</b>			
<b>Variable</b>	<b>Non-survivors (n)</b>	<b>Survivors (n)</b>	<b>p-value</b>
	Median (interquartile range)	Median (interquartile range)	
<b>PIM</b>	0.833 (0.515 - 0.967)	0.41 (0.230 - 0.677)	<0.001
<b>Duration of resuscitation (min)</b>	17.5 (10 - 30)	10 (5 - 15)	0.006
<b>Duration of intubation</b>	0 (0 - 2)	3 (1 - 7)	0.002
<b>ph</b>	7.07 (6.88 - 7.20)	7.22 (7.09 - 7.36)	0.001
<b>Chloride (mmol/l)</b>	109 (103 - 118)	104 (101 - 129)	0.027
<b>Creatinine (mmol/l)</b>	79 (45 - 118.5)	54 (34 - 72)	0.014
<b>Lactate (mmol/l)</b>	11.5 (5.2 - 15.7)	3.2 (1.4 - 6.8)	<0.001
<b>Number of adrenaline doses (0.1ml/kg of 1:10000)</b>			
0	13	23	0.6
1	7	14	0.7
2	7	6	0.2
3	5	4	0.6
4	3	3	0.9
5	3	9	0.7
6	2	4	0.7

Ten variables found to be associated with non-survival were included after adjusting for age and gender in stepwise backward logistic regression (Tab 9). None of the variable we were interested in were associated with outcome.

## DISCUSSION

### Incidence

This retrospective study of PICU admissions following cardiac arrest in a single tertiary center in South Africa showed an incidence of 2.2 per 1000 hospital admissions over the period under review. This figure is underestimation of the true incidence of all cardiac arrest in the hospital. We were unable to comment further on other cardiac arrest episodes or attempted CPR within the hospital wards that didn't survive to PICU admission since there are no source documentation or registry for such events.

Our study found male to female ratio of 1.49 to 1 but this had no impact on mortality outcome. Arrest episodes occurred predominantly in children under a year of age but not in the neonatal period, similar to other studies(46,47).

### Aetiology of cardiac arrest

Most of the patients in this study (69.8%) presented with no known underlying condition or co-morbidity. Respiratory, cardiac and gastro-intestinal disorders were the most common primary conditions related to cardiac arrest. We were unable to classify the precipitating cause of arrest into

hypoxia/asphyxia or circulatory shock(20,48). Our data showed respiratory diseases and gastro-intestinal diseases were more likely to be of an acute event whilst cardiac was more related to a chronic underlying condition. In our findings acute respiratory tract infections and other respiratory related causes were associated with hypoxia whilst gastro-intestinal diseases mostly acute diarrheal diseases probably resulted in circulatory failure or hypovolemic shock. (49,50).

Two studies looked at in-hospital cardiac arrest, one prospective in Brazil, Reis et al (48) and the other retrospective in Finland, Suominen et al (35) though limited to in-hospital cardiac arrest they included both arrest in all the wards and had similar data based on the Utstein style reporting. Whilst the latter might have had more resources and also with high literacy rate the former is a middle-income country with comparable characteristic to our study population the latter has comparable economic status as our population. In both studies the model of care and personnel managing patients with cardiac arrest were similar. As at the time of data collection in our study not all patients with cardiac arrest were on continuous monitoring device. We compared and contrasted outcomes of cardiopulmonary resuscitation of sustained return of spontaneous circulation. The Brazilian study reported hospital discharge outcome of 25.3%, the Finish study reported 63% whilst our study showed 55.3% survival to hospital discharge. Most common precipitating cause of cardiac arrest was cardiac (71% and 61% for the Finish and Brazilian studies respectively), whilst in our study hypoxia/asphyxia (26.9%) and circulatory and congenital cardiac condition accounted for 22.1% of arrests. Though cardiac arrhythmias, ventricular tachycardia and fibrillation were documented in 4.8%, we were unable to ascertain if they were the primary causes of cardiac arrest.

The study found that significant numbers of cardiac arrest episodes occurred during emergency endotracheal intubation and anesthetic procedures. Morray et al in their study looking at peri-operative cardiac arrest in children, found a significant proportion (69%) resulted from cardiovascular disease, the severity of underlying disease and drugs related to anesthesia. Review of our cases showed that there was a low level of senior staff supervision during arrest episode related to endotracheal intubation. However it must be noted that most of these patients were probably in peri-arrest status rather than technical incompetence of the personnel involved with intubation. The retrospective nature of this study means we are unable to interrogate this finding any further than noting that the circumstances involved severely ill children with compromised cardiovascular and respiratory conditions which increases the risk of cardiac arrest during endotracheal intubation and anesthesia. Even though from our data we were unable to determine if these arrests were due to pre-arrest states, it must be noted that endotracheal intubation particularly in very young sick children can be a high risk procedure and should not be left in the hands of junior staff.

### Duration of cardiopulmonary resuscitation

Cardiopulmonary resuscitation is the main treatment for cardiac arrest. Effective CPR with adequate depth of chest compression and rate alternating with ventilation and oxygen has significantly improved outcome of pediatric cardiac arrest.(51) There is not enough evidence to recommend when to terminate CPR and recent studies by Matos et al (n=3419 children) (52) and Goldberg et al (n=64339 adults) suggested that more patients may survive with longer duration of CPR than previously thought. It has been suggested that prolonged CPR may lead to poor neurological outcome in survivors. Five (5%) of the patients in our study had prolonged CPR, showing that in some cases providers are prepared to continue beyond the “usual” time frame to terminate CPR by convention. The reasons for prolonged resuscitation were not indicated in the patient hospital records. Our study did not find any association between duration of CPR and poor outcome. The data for unsuccessful cardiopulmonary resuscitation is not available for an overall look association of duration of resuscitation and poor outcome.

### Impact of cardiac arrest on neurological and other organ function

This study has shown that a large proportion of patients who had successful CPR with ROSC survived to discharge from hospital with reasonable neurological outcome as compared to about decade ago.(52, 53) The nature of this study did not allow for estimation of change in neurological status. Thirty eight (77.6%) had mild to normal POPC score, 5 (10 %) had severe disability. This is comparable to Meert et al in the PECARN study, a multi-cohort study reported (n=353) 76.7% of patients who survived to discharge had documented good neurological outcome (POPC score of 1, 2 or no change).

As with other studies(55) we found that shock was the most prevalent complication following an arrest, with acute kidney impairment and neurological impairment present in equal proportions.

### Limitations

This data is limited in that they were collected retrospectively with inherent inadequate documentation and capture resulting in missing data. As a result capture of some variables such as temperature and cardiac rhythm at cardiac arrest may not represent the true predictors of mortality but other variables were mostly well captured and the adopted analytical methodology addressed the concerns of missing data. As at the time of data collection not all the wards had patient monitors to monitor patients early.

Population based studies are necessary to determine incidence of out of hospital cardiac arrest. Our data was limited to the capture of only those participants who arrived at Red Cross War Memorial Children’s Hospital and admitted to PICU. We were therefore unable to determine the true incidence of OHCA.

Notwithstanding the limitations, this study gives insight into cardiac arrest in this population and the significance lies in its ability to elucidate epidemiology and outcome. It is only the first step in the process of finding out ways to prevent and treat pediatric cardiac arrest. Findings from studies such as ours may be used as a baseline or comparison for other studies, inform policy and implement targeted management of pediatric cardiac arrest.

## Conclusions

In this retrospective study we found the incidence of cardiac arrest preceding PICU admission with return of spontaneous circulation to be 2.2 per 1000 hospital admissions and almost two thirds were less than one year old. Acute respiratory failure, and circulatory failure from gastrointestinal and cardiac conditions were the most common underlying cause of cardiac arrest. Children undergoing emergency endotracheal intubation and anesthesia are at increased risk of cardiac arrest. Mortality was lower than predicted in children admitted to PICU following cardiac arrest. Most survivors had normal neurological function on hospital discharge.

## Recommendations

It is clear that an essential starting point for future research is the establishment of appropriate and comprehensive documentation of cardiac arrest episodes. Development of a cardiac arrest event registry with feedback to medical and nursing personnel would help to sensitize staff to the issues related to cardiorespiratory arrest episodes in children, and would help with documentation.

Patients on the wards who could potentially be at risk of cardiac arrest must be flagged and brought to the attention of staff on duty. Such patients could be nursed at the high dependency units or rooms on the wards.

We recommend that high risk patients should be identified and monitored in the appropriate setting with equipment, staffing and expertise to respond appropriately to any deterioration in clinical condition.

There is the need to strengthen supervision of junior staff who care for all at risk patients within the hospital especially those requiring procedures like intubation.

These interventions could potentially improve data collection, regular auditing and shaping of care of patients with the goal of identifying patients at risk early and institution of appropriate interventions to reduce its incidence.

## Acknowledgement

We thank all clinicians who were part of care of patients with cardiac arrest, staff of medical records and neuro-developmental clinic for the role in data collection and documentation and all the other members of the Pediatric Intensive Care Unit of the Red Cross War Memorial Children's Hospital, Cape Town.

## Authorship

Appiah JA, Salie MS, Morrow BM, Argent AC

## References

1. Topjian AA, Nadkarni VM, Berg RA. Cardiopulmonary resuscitation in children. *Curr Opin Crit Care*. 2009 Jun;15(3):203–8.
2. Donoghue AJ, Nadkarni V, Berg RA, Osmond MH, Wells G, Nesbitt L, et al. Out-of-hospital pediatric cardiac arrest: an epidemiologic review and assessment of current knowledge. *Ann Emerg Med*. 2005 Dec;46(6):512–22.
3. Straney LD, Bray JE, Finn J, Bernard S, Pilcher D. Trends in intensive care unit cardiac arrest admissions and mortality in Australia and New Zealand. *Crit Care Resusc*. 2014 Jun;16(2):104–11.
4. Efendijev I, Raj R, Reinikainen M, Hoppu S, Skrifvars MB. Temporal trends in cardiac arrest incidence and outcome in Finnish intensive care units from 2003 to 2013. *Intensive Care Med*. 2014 Dec;40(12):1853–61.
5. Chen J, Ou L, Hillman KM, Flabouris A, Bellomo R, Hollis SJ, et al. Cardiopulmonary arrest and mortality trends, and their association with rapid response system expansion. *Med J Aust*. 2014 Aug 4;201(3):167–70.
6. Bardai A, Berdowski J, van der Werf C, Blom MT, Ceelen M, van Langen IM, et al. Incidence, causes, and outcomes of out-of-hospital cardiac arrest in children. A comprehensive, prospective, population-based study in the Netherlands. *J Am Coll Cardiol*. 2011 May 3;57(18):1822–8.
7. Atkins DL, Everson-Stewart S, Sears GK, Daya M, Osmond MH, Warden CR, et al. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. *Circulation*. 2009 Mar 24;119(11):1484–91.
8. de Mos N, van Litsenburg RRL, McCrindle B, Bohn DJ, Parshuram CS. Pediatric in-intensive-care-unit cardiac arrest: incidence, survival, and predictive factors. *Crit Care Med*. 2006 Apr;34(4):1209–15.
9. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA*. 2006 Jan 4;295(1):50–7.
10. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part VI. Pediatric advanced life support. *JAMA*. 1992 Oct 28;268(16):2262–75.
11. Hartemann E, Floret D, Berthier JC, Durand F. [Cardiac arrest in children. Causes and future after cardiopulmonary resuscitation]. *Pediatric*. 1988;43(6):557–62.
12. Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, et al. Part 14: Pediatric Advanced Life Support 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010 Nov 2;122(18 suppl 3):S876–908.

13. The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: pediatric basic and advanced life support. *Pediatrics*. 2006 May;117(5):e955–77.
14. Zaritsky A, Nadkarni V, Hazinski MF, Foltin G, Quan L, Wright J, et al. Recommended guidelines for uniform reporting of pediatric advanced life support: the Pediatric Utstein Style. A statement for healthcare professionals from a task force of the American Academy of Pediatrics, the American Heart Association, and the European Resuscitation Council. *Resuscitation*. 1995 Oct;30(2):95–115.
15. Perlstein PH, Edwards NK, Sutherland JM. Apnea in premature infants and incubator-air-temperature changes. *N Engl J Med*. 1970 Feb 26;282(9):461–6.
16. Kleinman ME, Caen AR de, Chameides L, Atkins DL, Berg RA, Berg MD, et al. Part 10: Pediatric Basic and Advanced Life Support 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010 Oct 19;122(16 suppl 2):S466–515.
17. Madl C, Holzer M. Brain function after resuscitation from cardiac arrest. *Curr Opin Crit Care*. 2004 Jun;10(3):213–7.
18. Burne-Taney MJ, Kofler J, Yokota N, Weisfeldt M, Traystman RJ, Rabb H. Acute Renal Failure After Whole Body Ischemia Is Characterized by Inflammation and T Cell-Mediated Injury. *Am J Physiol Renal Physiol*. 2003 Jul 1;285(1):F87–94.
19. Bennett KS, Clark AE, Meert KL, Topjian AA, Schleien CL, Shaffner DH, et al. Early oxygenation and ventilation measurements after pediatric cardiac arrest: lack of association with outcome. *Crit Care Med*. 2013 Jun;41(6):1534–42.
20. Berg MD, Nadkarni VM, Zuercher M, Berg RA. In-hospital pediatric cardiac arrest. *Pediatr Clin North Am*. 2008 Jun;55(3):589–604, x.
21. Berg RA, Sanders AB, Kern KB, Hilwig RW, Heidenreich JW, Porter ME, et al. Adverse Hemodynamic Effects of Interrupting Chest Compressions for Rescue Breathing During Cardiopulmonary Resuscitation for Ventricular Fibrillation Cardiac Arrest. *Circulation*. 2001 Nov 13;104(20):2465–70.
22. Bennett KS, Clark AE, Meert KL, Topjian AA, Schleien CL, Shaffner DH, et al. Early Oxygenation and Ventilation Measurements After Pediatric Cardiac Arrest: Lack of Association With Outcome. *Crit Care Med*. 2013 Apr 2;
23. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials. *Resuscitation*. 2012 Apr;83(4):417–22.
24. Ferguson LP, Durward A, Tibby SM. Relationship between arterial partial oxygen pressure after resuscitation from cardiac arrest and mortality in children. *Circulation*. 2012 Jul 17;126(3):335–42.
25. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery

- and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation*. 2008 Dec;79(3):350–79.
26. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002 Feb 21;346(8):549–56.
  27. Testori C, Sterz F, Behringer W, Haugk M, Uray T, Zeiner A, et al. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation*. 2011 Sep;82(9):1162–7.
  28. Ferriero DM. Neonatal Brain Injury. *New England Journal of Medicine*. 2004;351(19):1985–95.
  29. Gunn AJ, Bennet L. Fetal hypoxia insults and patterns of brain injury: insights from animal models. *Clin Perinatol*. 2009 Sep;36(3):579–93.
  30. Neumar RW. Molecular mechanisms of ischemic neuronal injury. *Annals of Emergency Medicine*. 2000 Nov;36(5):483–506.
  31. Doherty DR, Parshuram CS, Gaboury I, Hoskote A, Lacroix J, Tucci M, et al. Hypothermia Therapy After Pediatric Cardiac Arrest. *Circulation*. 2009 Mar 24;119(11):1492–500.
  32. Young KD, Gausche-Hill M, McClung CD, Lewis RJ. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Pediatrics*. 2004 Jul;114(1):157–64.
  33. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, et al. Out-of-hospital cardiac arrest surveillance --- Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005--December 31, 2010. *MMWR Surveill Summ*. 2011 Jul 29;60(8):1–19.
  34. Nitta M, Iwami T, Kitamura T, Nadkarni VM, Berg RA, Shimizu N, et al. Age-Specific Differences in Outcomes After Out-of-Hospital Cardiac Arrests. *Pediatrics*. 2011 Oct 1;128(4):e812–20.
  35. Suominen P, Olkkola KT, Voipio V, Korpela R, Palo R, Räsänen J. Utstein style reporting of in-hospital paediatric cardiopulmonary resuscitation. *Resuscitation*. 2000 Jun;45(1):17–25.
  36. Rea TD, Page RL. Community Approaches to Improve Resuscitation After Out-of-Hospital Sudden Cardiac Arrest. *Circulation*. 2010 Mar 9;121(9):1134–40.
  37. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med*. 1997 Feb;23(2):201–7.
  38. Newborn C on F and. Apnea, Sudden Infant Death Syndrome, and Home Monitoring. *Pediatrics*. 2003 Apr 1;111(4):914–7.
  39. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009 Feb;37(2):666–88.
  40. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int*. 2007 May;71(10):1028–35.
  41. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: Post-Cardiac Arrest Care [Internet]. [cited 2013 May 9]. Available from: <http://circ.ahajournals.org>

42. McNarry A f., Goldhill D r. Simple bedside assessment of level of consciousness: comparison of two simple assessment scales with the Glasgow Coma scale. *Anaesthesia*. 2004 Jan;59(1):34–7.
43. Morrison LJ, Neumar RW, Zimmerman JL, Link MS, Newby LK, McMullan PW, et al. Strategies for Improving Survival After In-Hospital Cardiac Arrest in the United States: 2013 Consensus Recommendations A Consensus Statement From the American Heart Association. *Circulation*. 2013 Apr 9;127(14):1538–63.
44. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008 Jan;36(1):296–327.
45. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, Brodie-Fowler M. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. *Crit Care Med*. 2000 Jul;28(7):2616–20.
46. Tress E, Kochanek P, Saladino R, Manole M. Cardiac arrest in children. *Journal of Emergencies, Trauma, and Shock*. 2010;3(3):267.
47. Anesthesia-related Cardiac Arrest in Children: Initial Findi... : *Anesthesiology* [Internet]. [cited 2013 May 9]. Available from: [http://journals.lww.com/anesthesiology/Fulltext/2000/07000/Anesthesia\\_related\\_Cardiac\\_Arrest\\_in\\_Children\\_.7.aspx](http://journals.lww.com/anesthesiology/Fulltext/2000/07000/Anesthesia_related_Cardiac_Arrest_in_Children_.7.aspx)
48. Reis AG, Nadkarni V, Perondi MB, Grisi S, Berg RA. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. *Pediatrics*. 2002 Feb;109(2):200–9.
49. Chang P, Hsu HY, Chang MH, Lin FY. Shock in the pediatric emergency service: five years' experience. *Acta Paediatr Taiwan*. 1999 Feb;40(1):9–12.
50. Singh D, Chopra A, Pooni PA, Bhatia RC. A clinical profile of shock in children in Punjab, India. *Indian Pediatr*. 2006 Jul;43(7):619–23.
51. Topjian AA, Berg RA, Nadkarni VM. Pediatric Cardiopulmonary Resuscitation: Advances in Science, Techniques, and Outcomes. *Pediatrics*. 2008 Nov 1;122(5):1086–98.
52. Matos RI, Watson RS, Nadkarni VM, Huang H-H, Berg RA, Meaney PA, et al. Duration of Cardiopulmonary Resuscitation and Illness Category Impact Survival and Neurologic Outcomes for In-hospital Pediatric Cardiac Arrests. *Circulation*. 2013 Jan 29;127(4):442–51.
53. Young KD, Seidel JS. Pediatric Cardiopulmonary Resuscitation: A Collective Review. *Annals of Emergency Medicine*. 1999 Feb 1;33(2):195–205.
54. Slonim AD, Patel KM, Ruttimann UE, Pollack MM. Cardiopulmonary resuscitation in pediatric intensive care units. *Crit Care Med*. 1997 Dec;25(12):1951–5.
55. Checchia PA, Sehra R, Moynihan J, Daher N, Tang W, Weil MH. Myocardial injury in children following resuscitation after cardiac arrest. *Resuscitation*. 2003 May;57(2):131–7.



**APPENDICES**

**APPENDIX I: CASE RECORD FORM (CRF)**

Hosp ID:.....	Study ID:.....
Date of hospital admission: __/__/__	Time of admission: __ h __
Date of birth: __/__/__	Gender: M [ ]/F [ ]
Weight: ____ . __ kg	
Date of PICU admission: __/__/__	Time of PICU admission: __ h __
Reason for hospital admission:	
Diagnosis:.....	
PIM Score:.....	

<b><u>CARDIAC ARREST</u></b>	
Where did it occur?	
Out of hospital [ ], state where.....	
Time of health worker contact: __/__/__	Time arrival in hospital: __/__/__
In-hospital [ ] State where: Med Reg [ ]      Wards [ ]      Others [ ] State.....	
Date of cardiac arrest: __/__/__	Time of arrest: __/__/__
<b>Vital Signs at Cardiac Arrest</b>	

Sign	HR	RR	BP	Temp
LOC	A	V	P	U

<b>ECG:</b>	PEA [ ]	Asystole [ ]	VT/VF [ ]	Unknown [ ]
-------------	---------	--------------	-----------	-------------

**Circumstances Surrounding Arrest:**

1. Was it an expected arrest?      Yes [ ] No [ ]
2. Continued clinical deterioration Yes [ ] No [ ]
3. During a procedure (intubation) Yes [ ] No [ ]

**RESUSCITATION**

CPR: Y / N if Y state where? .....

Medication:

Drug	Date (dd/mm/yyyy)	Time given (hh:mm)	

Date resuscitation ended: \_\_/\_\_/\_\_\_\_ Time resuscitation ended: \_\_h\_\_

Intubated: Yes [ ] No [ ] Date of intubation: \_\_/\_\_/\_\_\_\_

**Physiological and Laboratory Status on admission to PICU**

	Temp	HGT	pH	K	Na	Cl	Mg	Ca	Urea	Creat	Lactate
Date											
Time											

**Post Arrest complication:**

1. Brain: Seizures [ ] persistent altered consciousness [ ] Focal signs [ ]

CT Brain: Yes [ ] No [ ] if Yes Date: \_\_/\_\_/\_\_\_\_

2. Renal failure Yes [ ] No [ ]

3. Acidosis Yes [ ] No [ ]

4. Shock Yes [ ] No [ ]

**Post Arrest Treatment:**

<b>Inotrope support:</b> Y [ ] N [ ]	<b>Ventilation support</b> Y [ ] N [ ]	<b>Date extubation</b> __/__/____
--------------------------------------	--	--------------------------------------

**ICU DISCHARGE STATUS**

Outcome: 1. Discharged to [Ward] [Home] [Rehab Facility] 2. Died [ ] Date: \_\_/\_\_/\_\_\_\_

Condition at discharge:

LOC	A	V	P	U
-----	---	---	---	---

Other impairment (state): .....

.....

.....

**WARD DISCHARGE STATUS**

Outcome: 1. Discharge [Home] [Rehab Facility] 2. Died [ ] Date: \_\_/\_\_/\_\_\_\_

Causes of death .....

Condition at discharge:

**Paediatric Overall Performance Category**

Score	Category (neuro function)	Description
1	Normal	Healthy, alert, regular class
2	Mild disability	Age appropriate interactions, but possible neurologic deficit, grade not appropriate
3	Moderate disability	Independent ADL but special education or learning deficit
4	Severe disability	Conscious but dependent on others because of neurologic deficit
5	Coma/vegetative state	Any degree of coma; unconscious; unaware
6	Dead	

**FOLLOW UP STATUS**

Date: \_\_/\_\_/\_\_\_\_

**Paediatric Overall Performance Category**

Score	Category (neuro function)	Description
-------	---------------------------	-------------

1	Normal	Healthy, alert, regular class
2	Mild disability	Age appropriate interactions, but possible neurologic deficit, grade not appropriate
3	Moderate disability	Independent ADL but special education or learning deficit
4	Severe disability	Conscious but dependent on others because of neurologic deficit
5	Coma/vegetative state	Any degree of coma; unconscious; unaware
6	Dead	

APPENDIX II



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences  
Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Ms S Ariefdien - Tel: [021]4066492 • Fax: [021]4066411  
email: sumayah.ariefdien@uct.ac.za

03 July 2012

HREC REF: 344/2012

**Dr JA Appiah,**  
Paediatric Intensive Care unit  
Red Cross War Memorial Children's Hospital  
Klipfontein Road  
Rondebosch  
7700

CC. Prof AC Argent  
Paediatric Intensive Care Unit  
Red Cross War Memorial Children's Hospital

Dear Dr Appiah,

**PROJECT TITLE: CARDIAC ARREST IN CHILDREN PRECEDING PICU ADMISSION: AETIOLOGY AND OUTCOME IN A DEVELOPING COUNTRY**

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

**Approval is granted until 28 July 2013**

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

**PROFESSOR MARC BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX III: RXH MPhil Approval



Email:  
thomas.blake@westerncape.gov.za  
Tel: +27 21 658 5788 fax: +27 21 658 5166  
18 February 2013

---

**DR JOHN APPIAH**

**PICU**

**RCWMCH**

Dear Dr Appiah,

**RE: RESEARCH**

Your request to do research in the PICU (CARDIAC ARREST IN CHILDREN PRECEDING PICU ADMISSION: AETIOLOGY AND OUTCOME IN A DEVELOPING COUNTRY) has been approved.

Kindly note that should you request folders from the Medical Records Department, that not more than five (5) folders may be removed at any one time. If they are removed, they must be returned before 16h00 on the same day.

Regards

**DR T A BLAKE**

**MANAGER MEDICAL SERVICES**

**RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL**

**RONDEBOSCH, 7700**

**021 658 5788 (T)**

**021 658 5166 (F)**

[thomas.blake@westerncape.gov.za](mailto:thomas.blake@westerncape.gov.za)

[www.westerncape.gov.za/english/gov/5981](http://www.westerncape.gov.za/english/gov/5981)



[www.westerncape.gov.za](http://www.westerncape.gov.za)



*Pediatric Critical Care Medicine* is an international, peer-reviewed journal that is interested in publishing the highest quality scientific studies in the field of pediatric critical care medicine.

## MANUSCRIPT SUBMISSION

Manuscripts are submitted through Editorial Manager®, a Web-based manuscript tracking system in use by SCCM. This system allows authors to add a new manuscript or check the status of a submitted manuscript, while shortening the time needed for processing manuscripts in the Editorial Office and through peer review. To submit manuscripts for consideration, go to [www.sccm.org](http://www.sccm.org), choose *Pediatric Critical Care Medicine* under the Publications tab, then select "Submit Manuscripts." Once you reach the Editorial Manager® home page, log on to the system by creating an account or entering through your existing account.

Editorial Manager® will easily guide authors through the manuscript submission process. Required information pertaining to the manuscript includes the name, address, telephone number, and e-mail address for the first author and all contributing authors; affiliated institutions; title of the manuscript; abstract; and key words. If authors wish, they may provide optional information that includes author's suggested reviewers and author's nonpreferred reviewers. The Editorial Office will automatically be notified of the submission and will send an e-mail confirming the submission of the manuscript to the author(s). After editorial office review of the submitted documents, a manuscript number will be assigned to each submitted manuscript, which will be used in all correspondence.

Each manuscript submission should designate one corresponding author and all contributing authors. The number of authors should be restricted to only those persons who have truly participated in the conception, design, execution, and writing of the manuscript. Authors must disclose any potential financial or ethical conflicts of interest regarding the contents of the submission.

SCCM accepts no responsibility for manuscripts that are lost or destroyed through electronic or computer problems. Authors are encouraged to keep copies of submitted manuscripts, including figures. If an author does not receive confirmation of submission into Editorial Manager® within two days, he or she should contact the Editorial Office at [journals@sccm.org](mailto:journals@sccm.org).

**Copyright.** Each author must complete and submit the journal's copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" ([www.icmje.org/update.html](http://www.icmje.org/update.html)). **The form must be completed by each author and must be uploaded with your other manuscript documents at the time of submission.** The form is readily available on the manuscript submission page <http://www.editorialmanager.com/pccm> and must be completed and submitted electronically. Please note that authors may sign the copyright transfer agreement form electronically. For additional information about electronically signing this form, go to <http://links.lww.com/ZUAT/A106>.

**Compliance With NIH and Other Research Funding Agency Accessibility Requirements.** A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

**Financial Disclosure and Conflicts of Interest.** Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional, and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding." For example:

Conflicts of Interest and Source of Funding: "Author A" has received honoraria from "Company 1." "Author B" is currently receiving a grant (#12345) from "Organization Y," and is on the speaker's bureau for "Organization X" – the CME organizers for Company 1. For the remaining authors none were declared.

**Human and Animal Subjects.** All studies of human subjects must contain a statement within the Materials and Methods section

indicating approval of the study by the Institutional Review Board (or institutional review body) that subjects have signed written informed consent, or that the Institutional Review Board waived the need for informed consent. **Before your submission can be sent out for peer review, it is necessary that you address this issue of institutional review approval.** This is in accordance with the International Committee of Journal Editors uniform requirements for manuscripts submitted to biomedical journals. Please see <http://www.icmje.org> for more details. All animal studies must contain a statement within the Materials and Methods section confirming approval by the Institutional Animal Care and Use Committee and that the care and handling of the animals were in accord with National Institutes of Health guidelines or other internationally recognized guideline for ethical animal treatment.

**Statistical Review.** Any study containing quantitative data and statistical inference should be reviewed by a consultant with formal statistical training and experience.

## MANUSCRIPT PREPARATION

Manuscripts must conform to *Pediatric Critical Care Medicine* Instructions for Authors and/or the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," which can be found on the International Committee of Medical Journal Editors Web site, [www.icmje.org](http://www.icmje.org). Manuscripts must be double-spaced with pages numbered consecutively, beginning with the title page. Each paragraph should be indented with a tab. The text portion of each manuscript should be in Microsoft Word format, including references and figure legends. Figures can be saved in .tif or .eps format in 300 dpi or higher. Tables should be submitted as Microsoft Word files; spreadsheets are not acceptable. Figures should be saved as separate files and uploaded after the text upload is complete. Specific guidelines for figure formatting are found on the Editorial Manager® home page. Documents submitted in .pdf format are not acceptable.

When uploading the text, tables, and figures into Editorial Manager®, there is the option of entering files for review and files for production. Files for review are viewable by the editorial staff, the editor, and the reviewers. These documents should include all text, tables, and figures, as well as any special referenced material. Files for production are only seen by the editorial staff and will not be seen by reviewers.

## MANUSCRIPT CONTENT

**Title Page.** The title page should contain 1) the title; 2) first name, middle initial, and last name of each author; 3) highest academic degrees, fellowship designations, and institutional affiliation for each author; 4) name of the institution(s) where the work was performed; 5) the address for reprints and a statement regarding whether reprints will be ordered; and 6) financial support used for the study, including any institutional departmental funds. The authors should also provide six key words for indexing, using terms from the Medical Subject Headings list of *Index Medicus*. Structured abstracts are required for all manuscripts (except editorials, letters, and book reviews) submitted to *Pediatric Critical Care Medicine*.

Editorial Manager® will prompt authors to input the above information into specific fields as they are submitting their manuscript. Authors should also upload their title page and structured abstract with the body of their manuscript. It is also important to note that if there is formatted text or Greek letters or symbols in the title or abstract, special coding is necessary and the Character Palette in Editorial Manager® will need to be used. *It is not necessary to code special characters and formats in the actual manuscript.*

**Abstracts.** Abstracts should be no more than 300 words in length and must have the following headings: Objective, Design, Setting, Patients (for Clinical Investigations) or Subjects (for Laboratory Investigations), Interventions, Measurements and Main Results, and Conclusions. Review papers and special articles should use these headings in the abstract: Objective, Data Sources, Study Selection, Data Extraction, Data Synthesis, and Conclusions. For details regarding the preparation of structured abstracts, refer to the *American Medical Association Manual of Style*, Tenth Edition (p. 20-23).

**Text Material.** The text should be organized into the following sections: Introduction, Materials and Methods, Results, Discussion, and Conclusions followed by Acknowledgments, References, Figure Legends, and Tables. Secretarial and editorial assistance are not acknowledged. Results may be presented in the text, in the figures, or in the tables. The Discussion section should interpret the results without unnecessary repetition. References to related studies should be included in the text section.

In addition, the following should be observed:

- The full term for which an abbreviation stands should be used at its first occurrence in the text unless it is a standard unit of measure. The abbreviation should appear in parentheses after the full term. Abbreviations should not be in the title, figure legends or table titles.

- For standard American units, do not use values that are more significant than your analysis is capable of accurately measuring (e.g., PaO<sub>2</sub> 84 torr [11.2 kPa], not 83.7 torr).
- Hemodynamic measurements for pressure (e.g., MAP) should appear in mm Hg and gas tension measurements (e.g., Po<sub>2</sub>) should appear in torr with SI units in parentheses. The units of vascular resistance are dyne·sec/cm<sup>5</sup>.
- Please provide r<sup>2</sup> values for parametric data.

**References.** All references should be cited in sequential order in the text and typed on a separate sheet of paper. References should be identified in text, tables, and legends by full-size Arabic numerals on the line and in parentheses. Do not use wordprocessing footnote, endnote, or paragraph numbering functions to make a list of references. Titles of journals should be set in italics and abbreviated according to the style used in *Index Medicus*. If journal titles are not listed in *Index Medicus* they should be spelled out. Unpublished data or personal communications should be noted parenthetically within the text but not in the References section. Inclusive page numbers (e.g., p. 1-10) should be used for all references. Listed below are samples of standard references; however, a complete listing of references can be found on the International Committee of Medical Journal Editors Web site, [www.icmje.org](http://www.icmje.org).

*Standard Journal Article:* Bone RC, Fisher CJ, Cemmer TP, et al: Sepsis syndrome: A valid clinical entity. *Crit Care Med* 1989; 17:389-393

*Standard Book with Authors:* Civetta JM, Taylor RW, Kirby RR. *Critical Care*. Third Edition. Philadelphia, Lippincott, Williams & Wilkins, 1996

*Standard Book with Editors:* Norman IJ, Refern SJ (Eds): *Mental Health Care for Elderly People*. New York, Churchill Livingstone, 1996

*Standard Chapter in a Book:* Phillips SJ, Whisnant JP: Hypertension and stroke. In: *Hypertension: Pathophysiology, Diagnosis and Management*. Laragh JH, Brenner BM (Eds). Second Edition. New York, Raven Press, 1995, pp 465-478

*Standard Web Site/Electronic Format:* Marion DW, Domeier R, Dunham CM, et al: Practice management guidelines for identifying cervical spine injuries following trauma. Available at: <http://www.east.org>. Accessed July 1, 2000

**Equations.** Equations should be created as normal text or as images. The use of equation editors or utilities may not convert correctly during the manuscript submission process and their use is discouraged.

**Tables and Figures.** The number of figures and tables should be appropriate for the length of the manuscript; do not use superfluous illustrations. Materials reproduced from another published source must be labeled "Reproduced with permission from..." In addition, a letter granting permission to reproduce the materials from the copyright holder must be received by SCCM when the manuscript is submitted for review. If the manuscript is accepted for publication, it will not be able to be printed unless this permission letter has been submitted. Adapted figure or table materials must be labeled "Adapted with permission from..." Letters of permission are also required for adapted materials. A sample of a permission request can be found on Editorial Manager® in the instruction section.

**Tables.** Do not use tabs to create tables and do not use table editors. Table building utilities will convert, providing that no special images were inserted. Do not reiterate tabular data in the text. Do not use abbreviations in table titles. Do not use all capital letters in table headings and text. Do not use center, decimal tab, and justification commands. Do not use spaces to separate columns. Use a single tab, not a space, on either side of the ± symbol. Do not underline or draw lines within tables. Footnoted information should be referenced using italicized, superscript, lower case letters (i.e., <sup>a,b</sup>) in alphabetical order (reading from left to right). Avoid lengthy footnotes and insert descriptive narratives in the text.

### Figures.

#### A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: <http://links.lww.com/ES/A42>
2. Create, scan, and save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
3. Upload each figure to Editorial Manager® in conjunction with your manuscript text and tables.

#### B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital art:

- Artwork should be saved as .tif or .eps files.
- Artwork is created as the actual size (or slightly larger) it will appear in the journal. (To get an idea of the size images should be when they print, study a copy of the journal to which you wish to submit. Measure the artwork typically shown and scale your image to match.)
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi.
- Photographs, radiographs, and other half-tone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.

- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

**Remember:**

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager® Web site and number figures consecutively in the Description box during upload.

For captions and variables within a figure, use Helvetica (or Arial) font, if possible, in upper and lower case letters. Radiographic prints must have arrows (if applicable) for clarity. Color photographs will occasionally be published in the journal if use of color is vital to making the point; authors will be charged the cost of color reproduction. Figures that do not conform to these specifications will be sent back to the corresponding author for correction.

Figure legends should contain enough information for the reader to understand the illustration without referring to the text, but should be concise and should not repeat information already stated in the text. Figure legends should be typed on a separate page. Figures must be referenced sequentially in the text. Authors must assume charges for changes made to figures after manuscripts are accepted.

**Units of Measure.** Authors should provide units of measurement in SI units. Authors should refer to the *American Medical Association Manual of Style*, Tenth Edition (p. 787) for details regarding SI units for laboratory data.

**Manufacturer.** Provide in parentheses the model number, name of manufacturer, their city, and state or country, for all equipment described in the paper.

**Drug Names.** Only generic drug names should be used. Trademark or brand names should not be used except in specific cases where the brand name is essential to reproduce or interpret the study. These exceptions should be noted in accompanying correspondence. The manufacturer with the city, state, and country must be provided for any brand name drugs.

**Permissions.** Any submitted materials that are to be reproduced (or adapted) from copyrighted publications must be accompanied by a written letter of permission from the copyright holder. Accepted manuscripts will be delayed if necessary permissions are not on file. A sample of a permission request can be found on Editorial Manager® in the instruction section.

**Supplemental Digital Content:** Authors may submit supplemental digital content to

enhance their article's text and to be considered for online-only posting. Supplemental digital content may include the following types of content: text documents, graphs, tables, figures, graphics, illustrations, audio, and video. Cite all supplemental digital content consecutively in the text. Citations should include the type of material submitted, should be clearly labeled as "Supplemental Digital Content," should include a sequential number, and should provide a brief description of the supplemental content. Provide a legend of supplemental digital content at the end of the text. List each legend in the order in which the material is cited in the text. The legends must be numbered to match the citations from the text. Include a title and a brief summary of the content. For audio and video files, also include the author name, videographer, participants, length (minutes), and size (MB). Authors should mask patients' eyes and remove patients' names from supplemental digital content unless they obtain written consent from the patients and submit written consent with the manuscript. Copyright and Permission forms for article content including supplemental digital content must be completed at the time of submission.

**Supplemental Digital Content Size and File Type Requirements:** To ensure a quality experience for those viewing supplemental digital content, it is suggested that authors submit supplemental digital files no larger than 10 MB each. Documents, graphs, and tables may be presented in any format. Figures, graphics, and illustrations should be submitted with the following file extensions: .tif, .eps, .ppt, .jpg, .pdf, .gif. Audio files should be submitted with the following file extensions: .mp3, .wma. Video files should be submitted with the following file extensions: .wmv, .mov, .qt, .mpeg, .mp4. Video files should also be formatted with a 320 x 240 pixel minimum-screen size. For more information, please review LWW's requirements for submitting supplemental digital content: <http://links.lww.com/A142>.

## MANUSCRIPT CATEGORIES

Guidelines for the most frequent types of articles submitted to the journal are summarized below.

**Clinical Investigations.** These include randomized controlled trials, case-control series, and retrospective studies, among others. Within this category, we also feature four subspecialty categories including: Cardiac Intensive Care, Neonatal Intensive Care, Neurocritical Care, and Quality and Safety. This category of manuscript has a word limit of 2000 to 4000 words (8-16 typed double-spaced pages) which includes an abstract of no more than 300 words; the Discussion section of the manuscript should be limited to no more than 1500 words; a maxi-

mum of 40 references; and no more than 7 Figures and/or Tables.

**Laboratory Investigations.** These include laboratory and animal research. This category of manuscript has a word limit of 2000 to 4000 words (8-16 typed double-spaced pages) which includes an abstract of no more than 300 words; the Discussion section of the manuscript should be limited to no more than 1500 words; a maximum of 40 references; and no more than 7 Figures and/or Tables.

**Review Articles.** These consist of critical assessment of literature and data pertaining to clinical topics. In review articles, emphasis should be placed on cause, diagnosis, prognosis, and prevention. Information concerning the type of study or analysis, population, intervention, and outcome should be included for all data used. The selection process used for all data should be described. Meta-analyses will be considered as review papers. The recommended length of review articles is 2000 to 3000 words (8-12 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 100 references; and no more than 10 Figures and/or Tables.

**Brief Reports.** These should be short reports of original studies or evaluations. The recommended length of brief reports is no more than 1500 words (6 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 25 references; and no more than 2 Figures and/or Tables.

**PCCM Perspectives.** These include articles that may fall outside the realm of formal clinical or basic science research, such as social policy, professional education, ethical dilemmas, and delivery of compassionate care. The recommended length is no more than 1500 words (6 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 25 references; and no more than 4 Figures and/or Tables.

**Evidence-Based Journal Club.** These articles provide an evidence-based critique of a recent important paper in the field of pediatric critical care medicine. The recommended length is no more than 1500 words (6 typed double-spaced pages) which includes an abstract of no more than 300 words; a maximum of 25 references; and no more than 4 Figures and/or Tables.

**Letters to the Editor.** Letters to the Editor are encouraged. Letters must specifically address a recent article published in *Pediatric Critical Care Medicine*. They should be no more than 500 words (2 typed double-spaced pages) with a maximum of 5 references.

**Invited Editorial.** These represent commentaries addressing newly published articles in the journal and are by invitation only. Invited editorials should be no more than 1200 words (5 typed

double-spaced pages) with a maximum of 15 references and a maximum of 2 Figures and/or Tables.

## EDITORIAL REVIEW

All manuscripts will be reviewed by Editorial Board members or consultants selected by the editor-in-chief. Initial editorial reviews usually are completed within 8-10 weeks of manuscript submission. The time required for review of revised manuscripts is variable.

## ACCEPTANCE

All information regarding the accepted manuscript and its publication date are confidential. No information regarding the manuscript can appear in print, on the television or radio, or in any electronic form until the day before its publication date. It cannot be released to the media until the day before the publication date.

Manuscripts accepted for publication are copy-edited and returned to the author for approval. Authors are responsible for all statements published in their work, including any changes made by the copyeditor. Authors are encouraged to proofread all edited manuscripts carefully. The

journal reserves the right to charge authors for excessive changes made to the text and figures at the page proof stage.

## Permissions

For permission and/or rights to use content for which the copyright holder is the Society of Critical Care Medicine or LWW, please go to the journal's Web site and after clicking on the relevant article, click on the "Request Permissions" link under the "Article Tools" box that appears on the right side of the page. Alternatively, send an e-mail to [customercare@copyright.com](mailto:customercare@copyright.com).

For Translation Rights & Licensing queries, contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. Email: [silvia.serra@wolterskluwer.com](mailto:silvia.serra@wolterskluwer.com).

For Special Projects and Reprints (U.S./Canada), contact Alan Moore, Director of Sales, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Phone: 215-521-8638. Email: [alan.moore@wolterskluwer.com](mailto:alan.moore@wolterskluwer.com).

For Special Projects and Reprints (non-U.S./Canada), contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical

Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: [silvia.serra@wolterskluwer.com](mailto:silvia.serra@wolterskluwer.com).

## REPRINTS

Reprints are available four weeks after the publication of the journal through the Publisher. For information and prices, call (800) 341-2258 or E-mail to [reprints@lww.com](mailto:reprints@lww.com).

## CONTACT

Questions regarding the status of submitted manuscripts are best answered by logging on to the FAQ section of Editorial Manager®. The assigned manuscript number will allow authors to view the status of their manuscript. If authors need additional information regarding a manuscript, please send an e-mail to [journals@sccm.org](mailto:journals@sccm.org) and include your manuscript number in the request, or call (847) 827-6869 Monday through Friday, from 0800 to 1700, Central Standard Time.

Correspondence can also be sent to: Patrick M. Kochanek, MD, MCCM Editor, *Pediatric Critical Care Medicine* Society of Critical Care Medicine 500 Midway Drive Mt. Prospect, IL 60056