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**Cefazolin plasma concentrations in children less than 25 kilograms  
undergoing elective cardiac surgery:  
An audit of current clinical practice at  
Red Cross War Memorial Children's Hospital**

by

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## DECLARATION

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## List of abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
CSF	Cerebrospinal fluid
CPB	Cardiopulmonary bypass
GFR	Glomerular filtration rate
ICU	Intensive care unit
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NSIPP	National Surgical Infection Prevention Project
RCWMCH	Red Cross War Memorial Children's Hospital
STS	Society of Thoracic Surgeons
SWI	Sternal wound infection
V <sub>d</sub>	Volume of distribution

## **Part A: Study protocol**

As approved by the Departmental Research Committee and Human Research Ethics Committee, University of Cape Town

University of Cape Town

## **1. Aims and objectives**

To evaluate whether, using the current antibiotic regimens, plasma concentrations of cefazolin remain above four times the minimum inhibitory concentration (MIC) for common pathogens for the intraoperative period in children undergoing elective cardiac surgery involving cardiopulmonary bypass (CPB).

Our secondary objectives are:

- To determine if the second dose should be given earlier than the current regimen of giving a second dose four to six hours after initial dose,
- To determine if the bypass pump should be routinely primed with a dose of cefazolin, as is the practice of some anaesthesiologists.
- To determine if a second dose is required during prolonged CPB

## **2. Background to study**

Our current antibiotic prophylaxis practice at Red Cross War Memorial Children's Hospital (RCWMCH) is to administer a dose of cefazolin 50 mg / kg of body weight at the time of induction of anaesthesia. This is followed by a second dose four to six hours later. It is also acceptable practice to add an additional dose (also 50 mg / kg) to the priming volume of the bypass pump, although not all cardiac anaesthesiologists routinely do this. Children weighing between 20 and 25 kg will receive a dose of 1000 mg. A further dose is given 6 hours later in the intensive care unit (ICU).

Our antibiotic prophylaxis for cardiac surgery at RCWMCH was previously cloxacillin and gentamicin, but it changed to cefazolin in 2009 in order to standardise the surgical prophylaxis across all disciplines. This was as per the microbiologists' advice and is in keeping with international practice (see 3.2 below). There was a cluster of sternal wound infection (SWI) at our institution in 2010, which led to a multidisciplinary investigation into the contributing factors. One of the factors was the concern around the choice of cefazolin as the sole antibiotic prophylactic agent and the dosing regimen. Other factors that were considered included the

preoperative preparation of the child, skin hygiene, ward protocols and theatre practice. No single cause was identified, but increased vigilance of the above factors has led to reduction in the incidence of SWI. The questions regarding the dosing regimen of cefazolin in children requiring cardiac surgery on CPB remain unanswered. The bacterial resistance patterns in our paediatric population have not changed recently, although some institutions are reporting an increase in methicillin-resistant *Staphylococcus aureus* (MRSA).

It is difficult to get an accurate incidence of SWI following elective cardiac surgery at RCWMCH. A formal audit of the current incidence has not yet been performed. Anecdotal evidence suggests that the incidence is within international standards of less than 5 %. There has not been an overall noticeable rise in the rate of surgical site infections at our institution.

The microbiology department at RCWMCH does not routinely collect data in this group of children. As their data is sorted according to the ward to which the patient is admitted, they are not able to isolate the data from this specific subset of children.

The morbidity and mortality from surgical site infections is significant and all measures should be taken to ensure the reduction in the incidence of postoperative sternal wound sepsis.

During CPB, the plasma levels of all drugs may be altered, due to, among other factors, the greater volume of distribution.<sup>1</sup> Cefazolin is a time-dependent antibacterial agent so its bactericidal action depends on the duration of time that the plasma concentrations are above the MIC for the causative bacteria.<sup>2</sup> Some sources suggest that the concentrations should remain above MIC for only 40 to 50 % of the dosing interval in treatment regimens.<sup>3</sup> As intraoperative contamination can occur at any point during surgery, it is suggested that the dosing regimen for prophylaxis should aim for plasma levels over MIC for 100 % of the surgical duration as well as for at least a few hours after closure of the skin incision.<sup>4</sup> Inadequate plasma concentrations of cefazolin in the perioperative period may contribute to the incidence of surgical site infection.

Our institution does not measure the MIC of sensitive microorganisms for cefazolin, as this drug is only currently recommended for surgical prophylaxis. Alternative antimicrobial agents are offered for treatment of postoperative wound infections, based on empirical data and then changed as necessary according to culture results.

This study may reveal that our current protocol produces ineffective plasma concentrations of cefazolin due to the effects of CPB. The findings from this research project could potentially lead to a more effective dosing regimen while on CPB.

### **3. Literature review**

#### **3.1 Sternal wound infections in paediatric cardiac surgery**

The incidence of SWI following cardiac surgery in the paediatric population is reported to be between 0.2 % and 4.8 %.<sup>5</sup> This is similar to that in the adult population. The limited published data in this population group is difficult to compare as the reported depth of SWI varies from superficial incisional to deep incisional to organ space infections.

Guidelines exist for the prevention of SWI for adult patients.<sup>6</sup> There are no equivalent international guidelines for paediatric patients, and various paediatric cardiac surgery centres have been using either adapted adult guidelines, or locally produced protocols.

The risk factors for SWI in children vary greatly from those in adults. In the adult population, diabetes, obesity and chronic obstructive pulmonary disease are some of the major risk factors for SWI.<sup>7</sup> Various risk factors have been shown to increase the chance of SWI in children. Edwards *et al.* showed that a pump bypass time of greater than one hour, excessive postoperative bleeding, a low cardiac output state for 24 to 72 hours postoperatively and re-exploration for the control of bleeding were all risk factors for the development of SWI.<sup>8</sup> They also proposed that inadequate antibiotic prophylaxis was an additional risk factor. Mehta *et al.* assessed risk factors for SWI in both elective and emergency paediatric cardiac surgery patients.<sup>9</sup>

They found an increased incidence of SWI in children of younger age, higher American Society of Anesthesiologists (ASA) score, longer preoperative stay, longer period of ventilation and inotropic support, longer stay on the ICU longer hospital stay and increased preoperative leucocyte band cell counts. Children with associated pre-existing conditions were also at an increased risk of SWI. Ben-Ami *et al.* showed three variables as independent risk factors for SWI: young age, cyanotic heart disease and prolonged central venous catheter dwell time.<sup>10</sup>

### 3.2 Prophylactic antibiotics in paediatric cardiac surgery

A review of perioperative antibiotic prophylaxis in paediatric cardiac surgery was published in 2007.<sup>11</sup> The choice of antibiotic, timing of dose and duration of therapy of prophylactic antimicrobials in paediatric cardiac surgery has been well debated. A meta-analysis of four placebo-controlled trials established antibiotic prophylaxis as the standard of practice in cardiac surgery, and concluded that further placebo-controlled trials would be unethical.<sup>12</sup> They also showed a reduction of SWI in patients treated with a cephalosporin, with an odds ratio of 0.51. Numerous comparisons between the first and second-generation cephalosporins have shown no statistical difference between the two groups.

Vancomycin appears to be no more effective than the cephalosporins in cardiothoracic surgical centres that have a lower incidence of MRSA infections.<sup>11</sup> Due to its side-effect profile, it is suggested that vancomycin be restricted to use in children with penicillin or cephalosporin allergies and in centres with a high incidence of MRSA.

There is insufficient evidence for the routine use of gentamicin as prophylaxis for cardiac surgery.<sup>11</sup>

The duration of the prophylaxis is debatable. General consensus is that antibiotic prophylaxis should not be continued for longer than 48 hours following major surgery. The Society of Thoracic Surgeons Workforce on Evidence Based Surgery suggested that a single dose prophylaxis might be adequate in cardiac surgery, but

there is inconclusive data.<sup>13</sup> An study involving 838 adult patients undergoing cardiac surgery showed a higher incidence of SWI in the group which only received a single dose at induction compared to a group which received multiple doses over the 24-hour postoperative period (8.3 % vs 3.6 %, p = 0.004).<sup>14</sup>

A retrospective review of three antibiotic prophylaxis regimens in paediatric cardiac surgical patients analysed three protocols used over a six-year period.<sup>15</sup> They showed a reduced incidence of SWI's in the group that received on-going prophylactic antibiotics until the chest tubes were removed. All their regimens used a dose of cefazolin of 50 mg / kg.

### 3.3 Cefazolin

#### 3.3.1 Microbial action

Cefazolin is a first generation cephalosporin, which was first evaluated for clinical use in the early 1970's.<sup>16</sup> It is a semi-synthetic derivative of cephalosporin C, with bactericidal activity against most gram-positive cocci (except enterococci and MRSA) and at higher concentrations against *Escherichia coli*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Salmonella* spp., and *Shigella* spp.

The breakpoint is the level of MIC at which a bacterium is deemed either susceptible or resistant to an antibiotic being used. If either the MIC of a particular strain or the MIC<sub>90</sub> of a group strain is found to be at or below this breakpoint, the organism(s) can be considered 'susceptible'. If it is above the breakpoint, it is deemed 'resistant'.<sup>3</sup> The most recent data on the pharmacokinetic and pharmacodynamic breakpoints of cefazolin for *Staphylococcus* spp. and *Enterobacteriaceae* spp. was published in January 2012.<sup>17</sup> The MIC<sub>90</sub> is the MIC below which 90 % of a group of organisms will show inhibited growth. The MIC<sub>90</sub> for sensitive *Staphylococcus* spp. is 8 mcg / mL, for intermediately-sensitive *Staphylococcus* spp. it is 16 mcg / mL and for resistant *Staphylococcus* spp. 32 mcg / mL. The MIC<sub>90</sub> for sensitive *Enterobacteriaceae* spp. is 2 mcg / mL for intermediately-sensitive *Enterobacteriaceae* spp. 8 mcg / mL and for resistant *Enterobacteriaceae* spp. 16 mcg / mL.

### 3.3.2 Pharmacokinetics

Cefazolin remains unchanged in the body, and about 80 – 100 % is excreted unchanged in the urine within 24 hours.<sup>18</sup> The serum half-life is 1.8 hours. It is 85 % protein bound. It is eliminated by renal excretion through passive filtration and active secretion.

### 3.4 Effects of CPB on cefazolin plasma concentrations

Adults undergoing elective cardiac surgery routinely receive 1 - 2 g of cefazolin intravenously 30 – 60 minutes prior to surgery.<sup>19</sup> There have been a number of trials in adults investigating the effects of CPB on cefazolin plasma concentrations.

Fellinger *et al.* looked at the serum cefazolin levels in 10 adults undergoing elective and urgent coronary artery bypass grafting. These patients received a dose of cefazolin at induction of anaesthesia (1 g) and a further dose immediately after onset of CPB. They found that the levels consistently remained above MIC<sub>90</sub> for *Staphylococcus aureus* and *Staphylococcus epidermidis*, but fell below the MIC<sub>90</sub> for *Enterobacter* spp., *Serratia* spp., *Escherichia coli* and *Proteus mirabilis*.<sup>20</sup>

A larger study divided 137 patients into 3 groups.<sup>21</sup> Group 1 received 1 g of cefazolin at the start of surgery and a second dose at the end of CPB. Group 2 received 2 g of cefazolin at the start of surgery and a continuous infusion of cefazolin at 20 mg per minute throughout surgery. Group 3 received 3 g of cefazolin at the start of surgery, followed by a continuous infusion of 15 mg per minute throughout surgery. Group 3 had statistically higher cefazolin concentrations at all time points when compared with Group 1 ( $p < 0.02$ ) and most time points when compared with Group 2 ( $p > 0.04$ ). This study suggested a larger pre-operative bolus, followed by a continuous infusion will result in higher serum and tissue concentrations. No related toxicity was reported.

Another study comparing an initial cefazolin bolus of 2 g followed by either further intermittent doses at 3, 9 and 15 hours, or a continuous infusion for 18 hours found that there were pharmacokinetic and pharmacodynamic advantages to the bolus plus

continuous infusion regimen.<sup>22</sup> They had 10 subjects in each group and measured blood and atrial myocardial tissue levels of cefazolin. They found that a larger initial dose, followed by the continuous infusion led to superior serum and tissue concentrations, at all intraoperative intervals, with no related toxicity or adverse events.

The effects of profound hypothermic arrest have also been studied.<sup>23</sup> Four groups of 10 patients receiving cefazolin prophylaxis were studied. Group A underwent vascular surgery without CPB. Group B had cardiac surgery with CPB time of less than 120 minutes. Group C had cardiac surgery with a CPB time of greater than 120 minutes and Group D had cardiac surgery with profound hypothermic circulatory arrest. They all received cefazolin at induction and a second dose before wound closure. Their plasma concentrations of cefazolin were measured at set intervals during surgery. Patients in Group A had levels above 16 mcg / mL throughout surgery. Group B had levels above the MIC for sensitive *Staphylococcus aureus* (8 mcg / mL), but below 16 mcg / mL for 30 % of the time. Group C patients had levels below 8 mcg / mL in 50 % of patients. Group D showed better levels, and only one patient had levels below inhibitory concentrations. They concluded that their regimen was generally suboptimal and recommended further studies to investigate a more suitable protocol, but patients undergoing profound hypothermic circulatory arrest are better protected.

O'Rullian *et al.* investigated whether the use of ultrafiltration at the end of CPB had an effect on cefazolin levels.<sup>24</sup> This was a small study, which included five adult patients who received ultrafiltration after CPB and six patients who had CPB without ultrafiltration. They analysed three blood samples from each case. They showed no significant variation between the plasma levels in the two groups, concluding that ultrafiltration does not affect the serum levels of cefazolin. The limitations of this trial were due to its small sample size and only three sampling points in each case.

A study investigating cefazolin levels in children undergoing CPB was published in 2003.<sup>25</sup> Haessler *et al.* performed a prospective study of 19 infants weighing less than 10 kg, undergoing cardiac surgery requiring CPB. These children received 40 mg / kg of cefazolin, and gentamicin 5 mg / kg at induction of anaesthesia and

further doses of cefazolin 35 mg / kg every 8 hours and gentamicin 2 mg / kg every 12 hours for a total of 48 hours. They showed adequate levels of cefazolin throughout the perioperative period on this regimen, although the peak gentamicin levels were high intraoperatively. They commented that their study had limited postoperative samples.

#### **4. Scientific design**

The study will be a non-interventional observational prospective study of 15 to 20 children undergoing elective cardiac surgery requiring CPB at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town.

The study will be conducted in accordance with the South African Good Clinical Practice Guidelines and the Declaration of Helsinki.

Patients will all receive standard perioperative anaesthetic and surgical care, according to the current practice at RCWMCH.

An initial dose of cefazolin 50 mg / kg of body weight will be administered as an intravenous infusion over one minute, following induction of anaesthesia, via a peripheral intravenous line. A second dose (50 mg / kg) can be given four to six hours after the first dose. This may occur intraoperatively during CPB or postoperatively on the ICU. Two of the cardiac anaesthesiologists routinely add a further dose of cefazolin (50 mg / kg) to the CPB circuit prior to going on bypass. The administration of the second dose will be documented and these children will be analysed in a subset group. This is the current accepted antibiotic prophylaxis regimen at our institution. There will be no change to the current standard of care. The children will not be randomised to either group.

To assay plasma concentrations of cefazolin, blood samples will be drawn from the intra-arterial catheter that is placed routinely in either the femoral or radial arteries after induction of anaesthesia. Most similar studies have used arterial samples.<sup>25,26,27</sup> This will avoid any possible contamination of the sample by the venous

administration of the dose. Each sample will not exceed 0.5 mL in volume. All children undergoing cardiac surgery will have an arterial catheter placed, so this study will not require any additional invasive lines. The total volume of blood drawn from each subject will not exceed 8 mL (16 samples). Most children will have 13 to 16 samples.

A baseline sample will be taken prior to the first dose of cefazolin. The second dose will be taken three minutes after the completion of the initial dose infusion. This will determine the peak plasma concentration after the intravenous bolus of cefazolin. The third sample will be taken at the time of sternal incision. The fourth sample will be taken at the immediately prior to commencement of CPB (at the time of cannulation of the aorta). The fifth sample will be taken once full flow CPB is established. Further samples will be taken every 30 to 60 minutes while on CPB, and immediately before the end of CPB. The next sample will be once off CPB, at skin closure, and then immediately prior to the next dose of cefazolin (trough level), four to six hours after the initial dose.

In order to perform future pharmacokinetic studies of the effects of CPB on cefazolin plasma concentrations, a control population is required. Following the second dose of cefazolin in the ICU, a peak level will be measured, and then two to three further samples at one to four hours post dose. This is to reduce the variables, which contribute to pharmacokinetic differences between individuals and accurately determine the actual effects of the CPB.

The samples will be stored on ice for a maximum of six hours and then centrifuged by the principal investigator. The plasma will be stored at minus 70 degrees centigrade. These samples will initially be stored at the laboratory at RCWMCH, and then moved to the Department of Pharmacology at the University of Cape Town, where they will be analysed. The storage facilities and transport arrangements have been assessed by the Department of Pharmacology as being both valid and adequate for the samples concerned.

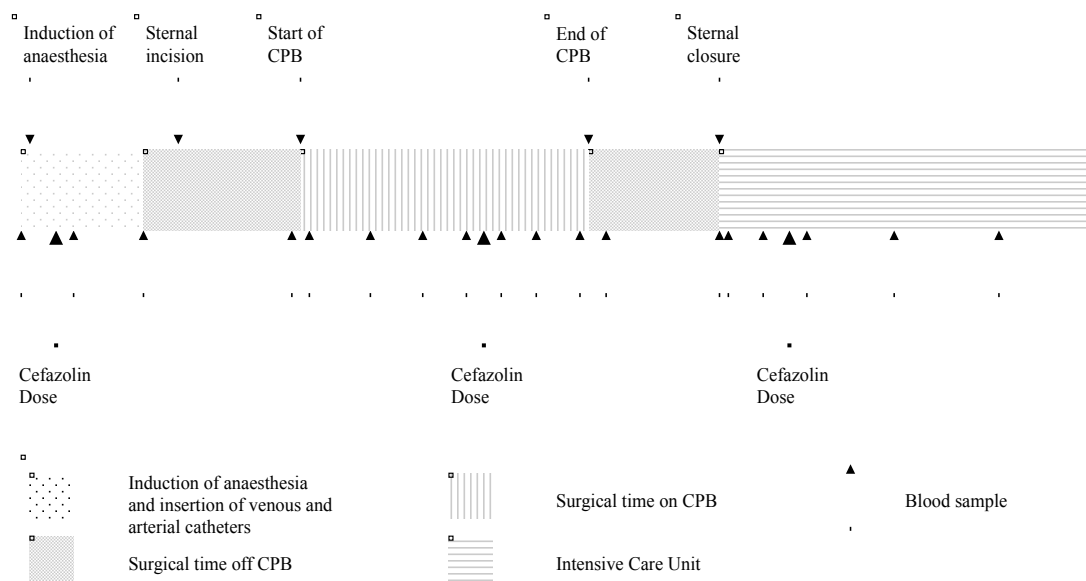


Figure 1: Time course of antibiotic administration and blood samples

## 5. Subject selection

The study will include up to 20 consecutive children with a body weight of less than 25 kg, undergoing elective cardiac surgery requiring cardiopulmonary bypass.

Valid informed consent will be obtained from the child's parent or legal guardian, once eligibility for the study has been confirmed. The principal investigator will personally obtain informed, written consent from the child's legal guardian or parent. This interview will take place on the day prior to the elective surgery. Adequate time will be spent with the parent, allowing full explanation of the planned procedures and time for questions to be answered adequately. An information leaflet will be provided in English, Afrikaans or isiXhosa, and the consent form will also be available in these languages. The parent or legal guardian will be informed that their consent can be withdrawn at any stage and that this will not compromise the care of their child in any way. An independent witness will be present during the consent interview to ensure the absence of undue influence and coercion.

There will be no financial re-imburement to the study subjects.

The inclusion criteria are as follows:

- 1) Body weight of less than 25 kilograms
- 2) Elective cardiac surgery requiring CPB
- 3) Valid informed consent from the parent or legal guardian to participate in the study and to store specimens for immediate and future analysis

The exclusion criteria are as follows:

- 1) Expected CPB time of less than 30 minutes
- 2) History of allergy to penicillin or cephalosporins
- 3) Pre-existing renal or hepatic dysfunction
- 4) Exposure to any antimicrobial agent within the previous week
- 5) History of a recent infection

## **6. Measurement and statistical analysis**

The blood samples will be sent to the University of Cape Town's Pharmacology Department, where they will be analysed. This department is currently developing an appropriate assay to measure the cefazolin plasma levels. The reference standards have been purchased, and the assay method will be validated according to international standards. The measurement will be by liquid chromatography and mass spectrometry.

This is a non-interventional, observational study and not a comparison between treatment modalities so a power calculation is not necessary.

Any documented SWI during the 14 postoperative days will be recorded. The patient's clinical record will be used to assess the nature of the wound infection, the results of any microbiological tests performed and the antibiotic therapy required. This is purely for descriptive purposes as the sample size is inadequate to make any clinically or statistically significant conclusions.

The plasma concentrations profiles will be interpreted with non-linear mixed-effects modelling, using the software NONMEM<sup>®</sup>. This technique is largely used in the analysis of pharmacokinetic and pharmacodynamic data and provides a model-based

semi-mechanistic explanation for the changes in drug concentration. Moreover, it is able to identify and quantify the separate sources of variability in the data, such as measurement error and the physiologically driven differences in parameter values between subjects. Body size, renal function, age, gender and other relevant co-variates will be tested as predictors for the between subject variability and integrated in the model if found significant. The pharmacokinetic model will then be used for simulation of confidence intervals and will provide a platform to investigate different dosing scenarios and optimize the drug administration.

Statistical analysis will be done using Stata<sup>®</sup> data analysis and statistical software. A histogram will be used for each variable to test for normality. A p-value of less than 0.05 will be considered to be statistically significant.

## **7. Additional data collection**

The following data will also be collected from each study subject:

1. Age, gender, height and weight
2. Type of surgery performed and details of cardiopulmonary bypass (duration of CPB and aortic cross-clamp)
3. Concurrent medication
4. Co-morbidities
5. All drugs administered during surgery
6. All intravenous fluids and blood products administered during surgery
7. Serum haematocrit values throughout surgery (routinely tested on arterial blood gas analysis)
8. Anatomical site of intravenous and intra-arterial catheters
9. Type and volume of cardioplegia used
10. Preoperative renal function and estimated glomerular filtration rate (using the Schwartz formula).
11. Any evidence of SWI in the first 14 days following surgery (documented wound infection in patient records by the cardiothoracic surgical team, pus swab and blood culture results and the need for additional antimicrobial therapy during this period)

## **8. Confidentiality**

The consent form will bear the child's name and date of birth, but this information will be kept in a safe, locked location. Further identification of the samples will be by means of a unique number, which will correspond to each subject.

## **9. Conflicts of interest**

There are no conflicts of interest to declare.

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## **Part B: Structured literature review**

## **1. Objectives of literature review**

The main objectives of this literature review are to critically review the current published literature about cefazolin pharmacokinetics, including the influence of cardiopulmonary bypass (CPB) on cefazolin plasma concentrations, and to evaluate the drug's usage and dosing regimens as a prophylactic antibiotic in paediatric cardiac surgery. Published paediatric data is limited in this field and thus consideration and extrapolation of data from the adult population data will be required.

## **2. Literature search strategy**

A PubMed literature search was performed, using the free text and MeSH thesaurus terms 'cefazolin' or 'cephalosporin' with 'cardiac surgery', 'cardiopulmonary bypass', or pharmacokinetics'; as well as 'cardiac surgery' with 'sternal wound infections', 'antibiotic prophylaxis'. Both adult and paediatric data was reviewed, with an emphasis placed on paediatric literature. Literature published between January 1970 and December 2012 was included. Literature was excluded from the review if it had not been originally published in the English language.

## **3. Review and critical appraisal of the literature**

### **3.1. Pharmacological properties of cefazolin**

Cefazolin is a semi-synthetic first generation cephalosporin that was developed in the 1970's. It has enjoyed widespread use, initially as a therapeutic antimicrobial agent and more recently as the recommended prophylactic antibiotic for many surgical procedures.

Cefazolin can be administered either by the intramuscular or the intravenous route. The drug remains unchanged in the body and is excreted by the kidneys via both

passive filtration and active secretion. The plasma half-life is 1.8 hours and it is 85 % protein-bound.<sup>1</sup>

The adverse effects of cefazolin are limited to allergic phenomena and mild symptoms of nausea and burning on injection. In experimental animal studies, cephalosporins have been shown to cause damage to proximal renal tubular cells.<sup>2</sup> The only published human cases of possible cefazolin toxicity suggested that high cerebrospinal fluid concentrations (CSF) of cefazolin (34 – 106 mcg / mL) were associated with seizures in three adult patients.<sup>3</sup> No reference range exists for CSF cefazolin concentrations, and the correlated serum levels were 360 – 1000 mcg / mL.

Gram-positive cocci (with the exception of enterococci and methicillin-resistant staphylococci) are generally susceptible to cefazolin. Of the gram-negative bacilli, only *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella* spp. and *Shigella* spp. are modestly sensitive to cefazolin.<sup>1</sup> The remaining gram-negative organisms are generally resistant.

The minimum inhibitory concentration (MIC) of an antimicrobial is defined as the lowest concentration that will inhibit visible growth of a microorganism after overnight incubation in a culture medium. By contrast, the minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial that will prevent growth of the organism, after subculture onto antimicrobial free media.<sup>4</sup>

Reller *et al.* investigated the clinical efficacy of cefazolin as a therapeutic antibiotic, and measured the MIC and MBC for common significant pathogens.<sup>5</sup> In this study, the MIC of cefazolin for 30 isolates of *Staphylococcus aureus* ( $10^4$  organisms / mL) (both penicillin-sensitive and penicillin-resistant) was found to be less than 1 mcg / mL. Higher inocula of organisms ( $10^6$  organisms / mL) showed a higher MBC of 25 mcg / mL. The gram-negative pathogens also showed a striking increase of the MBC with increasing size of inoculum. However, these higher inocula are not likely to be relevant when cefazolin is used as a prophylactic antibiotic.

As with the other cephalosporins, the action of cefazolin is by time-dependent killing.<sup>6</sup> This implies that the inhibitory effect of the antibiotic is dependent on the time that the plasma concentration remains above the MIC during the dosing interval. The interstitial fluid concentration is in rapid equilibrium with the serum concentration and the bacteria are exposed to external cellular membranes that are in contact with the interstitial fluid. Serum concentrations have, therefore, been correlated to *in vivo* bactericidal action. The extracellular tissue fluid protein content is about one-third of that of the serum. While the free fraction of cefazolin will be in equilibrium between these fluid compartments, the total concentration of a highly protein-bound drug will be lower in the tissue fluid.<sup>7</sup>

The required time above MIC varies according to pathogen, infection site and drug. It is generally accepted that the serum levels should be above MIC for 40 to 50 % of the dosing interval when used for therapeutic goals.<sup>8</sup> In a study characterising the relationship between gentamicin levels during surgery and postoperative wound infections in colorectal surgery, the gentamicin plasma concentration at time of skin closure was one of the strongest independent risk factors for infection.<sup>9</sup> As intraoperative contamination can occur at any point during surgery, it is suggested that the dosing regimen should aim for plasma levels over MIC for 100 % of the surgical duration as well as for at least a few hours after closure of the skin incision.<sup>10</sup>

Some data suggests that in order to ensure maximal time-dependent killing and prevent the development of resistance, a serum concentration at least four times the MIC is targeted.<sup>7</sup> These studies were conducted both *in vitro* and *in vivo*; however, the goal was for eradication of an existing micro-organism, not specifically for antibiotic prophylaxis.

The breakpoint is the level of MIC at which a bacterium is deemed either susceptible or resistant to an antibiotic being used. The most recent data on the pharmacokinetic and pharmacodynamic breakpoints of cefazolin for *Staphylococcus* spp. and *Enterobacteriaceae* spp. was published in 2012.<sup>11</sup> If either the MIC of a particular strain or the MIC<sub>90</sub> of a group strain is found to be at or below this breakpoint, the

organism(s) can be considered 'susceptible'. If it is above the breakpoint, it is deemed 'resistant'.<sup>8</sup> The MIC<sub>90</sub> is the MIC below which 90 % of a group of organisms will show inhibited growth. The MIC<sub>90</sub> for sensitive *Staphylococcus* spp. is 8 mcg / mL, for intermediately sensitive *Staphylococcus* spp. it is 16 mcg / mL and for resistant *Staphylococcus* spp. 32 mcg / mL. The MIC<sub>90</sub> for sensitive *Enterobacteriaceae* spp. is 2 mcg / mL for intermediately-sensitive *Enterobacteriaceae* spp. 8 mcg / mL and for resistant *Enterobacteriaceae* spp. 16 mcg / mL.

### 3.2. Effect of cardiopulmonary bypass on cefazolin plasma concentrations

CPB can affect the pharmacokinetics and pharmacodynamics of drugs for a variety of reasons. An increased volume of distribution (with resultant haemodilution), altered protein binding, decreased elimination, reduced organ perfusion and hypothermia are the main factors.<sup>12</sup>

Miller *et al.* considered the effect of CPB on cefazolin pharmacokinetics.<sup>13</sup> This study had a small sample size of eight adult patients. They found there was an initial decrease in the serum concentrations after initiation of CPB, due mainly to haemodilution, followed by a plateau or gradual rise in the levels, due to redistribution of the drug. When comparing the differences in renal clearance measured during the pre-bypass, bypass and post-bypass intervals, no significant difference was found. This was a very small study, so statistical significance would not have been achieved.

There is limited published data on the alterations to the pharmacokinetic properties of drugs in the paediatric population. The volume of distribution ( $V_d$ ) of a drug is determined by the extent to which the drug penetrates the extravascular compartment. In neonates, the total body weight consists of 80 % water, which then decreases over the following four months of life to around 60 %, similar to that of an adult. Hydrophilic drugs such as cefazolin have an increased apparent  $V_d$  in this age group. For a drug to leave the central, intravascular compartment, it must be in its

free, unbound form. The protein-binding capacity of a neonate is also immature, and with lower circulating levels of albumin and other plasma proteins an increased free fraction of the drug can be anticipated.<sup>14</sup>

As cefazolin is excreted unchanged in the urine, the clearance of the drug is dependent on the glomerular filtration rate (GFR). The GFR is reduced in neonates, reaching and exceeding adult levels in the first few years of life. By six to eight years of age, a child's GFR matches an adult's GFR. This variation in GFR would lead to increased plasma levels of cefazolin in the neonatal population, but reduced levels between the ages of two to six years.<sup>14</sup> To date, no pharmacokinetic studies have been conducted that look at the renal clearance of cefazolin in the paediatric population. A study conducted in adults undergoing cardiothoracic surgery (of which only 44 % of the cases involved CPB) showed there was a strong negative correlation between a preoperative creatinine clearance of less than 50 mL / min and time above MIC. A shorter postoperative dosing interval of less than six hours was recommended in order to achieve 100 % time above MIC in patients with normal renal function.<sup>15</sup> This study showed an increase in postoperative surgical site infections in the group with a normal preoperative creatinine clearance, but this was not statistically significant.

The effect of hypothermia on serum cefazolin levels was investigated in a prospective study by Caffarelli *et al.*<sup>16</sup> This study found that serum cefazolin levels were not affected by a CPB duration of less than 120 minutes with mild to moderate hypothermia. In cases requiring CPB times of longer than 120 minutes, the plasma levels dropped to ineffective therapeutic levels in 50 % of patients. Profound hypothermic circulatory arrest appeared to have a slightly protective effect on the serum levels. Although these cases also had prolonged CPB times, only 10 % of patients had a sub-therapeutic plasma level. This is possibly due to the delayed renal excretion that can occur at low body temperatures.

### 3.3. Sternal wound infection in paediatric cardiac surgery

SWI is a significant cause of morbidity and mortality following elective paediatric cardiac surgery. The incidence of SWI following cardiac surgery in the paediatric population varies between 0.2 % and 4.8 %.<sup>17,18,19</sup> This is similar to that in the adult population, which is well reported to be between 0.5 % and 7.4 %.<sup>20,21,22</sup> The limited published data in this population group is difficult to compare as the reported severity of SWI varies between studies. SWI following cardiac surgery can be classified as either superficial or deep. Superficial infections are limited to the skin (superficial incisional) or to the soft tissue overlying the sternum (deep incisional), while deep infections extend to the sternum and / or mediastinum.

International guidelines exist for the prevention of SWI in adult cardiac patients.<sup>23</sup> As well as antibiotic prophylaxis, these guidelines also address hand hygiene, blood glucose control, the avoidance of preoperative shaving of the surgical field, strict surgical skin asepsis, surgical techniques and postoperative wound care. Reducing the microbial load by preoperative showering is recommended, and nasal decolonization in patients with proven nasal carriage of *Staphylococcus aureus* is shown in some papers to be effective in reducing SWI, but the literature is unclear. There are no equivalent international guidelines for paediatric patients, and paediatric cardiac surgery centres use adapted adult guidelines, or local protocols.

#### 3.3.1. Risk factors for sternal wound infection

The risk factors for SWI in children vary greatly from those in adults. In the adult population, diabetes, obesity, previous myocardial infarction and chronic obstructive pulmonary disease represent some of the major risk factors for SWI.<sup>24</sup> Owing to differing disease profiles, these risk factors are not generally transferable to the paediatric population.

Various risk factors have been shown to increase the chance of SWI in children. Mehta *et al.* assessed risk factors for SWI in both elective and emergency paediatric cardiac surgery patients.<sup>25</sup> This was a retrospective chart review of 202 children

following cardiac surgery, with an incidence of SWI of 5 %. They found an increased incidence of SWI in children with younger age (mean 4.7 months), higher ASA score, longer preoperative stay, longer period of ventilation and inotropic support, longer intensive care unit stay, longer hospital stay and increased leucocyte band cell counts preoperatively. Children with associated pre-existing conditions were also found to be at an increased risk of SWI.

Ben-Ami *et al.* demonstrated three significant independent risk factors for SWI: young age (less than nine months of age), cyanotic heart disease and prolonged central venous catheter dwell time.<sup>26</sup> This was also a retrospective chart review of 1821 patients, with an incidence of SWI of 2.7 %.

A further retrospective case-control study of 1017 children showed paediatric cardiac patients showed weight (less than 4.5 kg), age (less than 2.5 months) and ASA score (greater than 3) to be significant and strongly correlated risk factors for SWI. Interestingly, the administration of antibiotic prophylaxis within 60 minutes of start of surgery was not a significant risk factor. The rate of compliance with local timing guidelines for antibiotic prophylaxis was low in both groups (case group 50 % and control group 62 %).<sup>19</sup>

### 3.3.2. Causative organisms

Coagulase-negative staphylococci or methicillin-sensitive *Staphylococcus aureus* are isolated in the majority of both deep and superficial SWI.<sup>19,25,26,27</sup>

In some centres, methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming more prevalent.<sup>24</sup> Filsoufi *et al.* found that gram-negative organisms are cultured in up to 59 % of cases of mediastinitis, of which the most prevalent isolates were *Pseudomonas* spp., *Acinetobacter* spp. and *Enterobacter* spp.<sup>24</sup> Culture-negative SWI account for up to 15 % of cases in some studies.<sup>27</sup>

### 3.4. Antibiotic prophylaxis in paediatric cardiac surgery

A review of perioperative antibiotic prophylaxis in paediatric cardiac surgery was published in 2007.<sup>28</sup> The choice of antibiotic, timing of dose and duration of therapy of prophylactic antimicrobials has been well debated. A meta-analysis of four placebo-controlled trials established antibiotic prophylaxis as the standard of practice in cardiac surgery, and concluded that further placebo-controlled trials would be unethical.<sup>29</sup> They also showed a reduction of SWI in patients treated with a cephalosporin, with a summary odds ratio of 0.51. Numerous comparisons between the first- and second-generation cephalosporins have shown no statistical difference between the two groups.<sup>28</sup>

Vancomycin appears to be no more effective than the cephalosporins in cardiothoracic surgical centres with low levels of MRSA infections.<sup>28</sup> Due to its side-effect profile, it is suggested that vancomycin be restricted for use in children with penicillin or cephalosporin allergies and in areas with a high incidence of MRSA.

There is insufficient evidence for the routine use of gentamicin as prophylaxis for cardiac surgery.<sup>28</sup>

Three organisations, the National Surgical Infection Prevention Project (NSIPP), the Society of Thoracic Surgeons (STS) and the American College of Cardiology / American Heart Association (ACC / AHA) have published guidelines for antibiotic prophylaxis in adult cardiac surgery regarding antibiotic choice, dose and duration of surgery.<sup>30,31,32,33</sup> These adult guidelines recommend cefazolin or cefuroxime as the antibiotic of choice for patients without a beta-lactam allergy. A total duration of less than 24 to 48 hours is suggested. The first dose should be given within 30 to 60 minutes before surgical incision. The NSIPP recommends repeated doses intraoperatively if surgery is still in progress after two half-lives following the first dose. The STS recommends a second dose every three to four hours during surgery.

#### 3.4.1. Dosing regimens for cefazolin in paediatric cardiac surgery

The duration of sternal wound infection prophylaxis is debated. General consensus is that antibiotic prophylaxis should not be for longer than 48 hours following major surgery, but some cardiac centres continue prophylaxis until all chest tubes and central venous lines are removed. There are no large randomised prospective trials specifically evaluating the duration of prophylaxis in paediatric cardiac surgery. Higher doses and prolonged duration of administration of antibiotics is associated with higher medical costs and the development of antimicrobial resistance.<sup>34</sup>

A prospective observational study of the optimal duration of antibiotic prophylaxis for cardiac surgery in adults compared an initial regimen of administering a dose of cefazolin at induction of anaesthesia, and one further intraoperative dose, with a new regimen of continuing cefazolin for 24 hours postoperatively.<sup>35</sup> This study concluded that there was no difference in the 30-day or 6-month mortality between the two groups, so increasing the duration of prophylaxis did not result in a significant reduction in deep SWI. They also found lower compliance with the new 24-hour regimen, possibly due to some physicians' reluctance to give a repeat intraoperative dose.

A randomised prospective study including 838 adult cardiac patients receiving either a single dose at induction or a 24-hour treatment, showed that the single-dose regimen was associated with an increased incidence of SWI (8.3 %) compared with the 24-hour regimen (3.6 %) ( $p = 0.004$ ).<sup>36</sup> They included both superficial and deep or organ space SWI. There was no difference in mortality or duration of hospitalisation.

A retrospective review of antibiotic prophylaxis regimens in nearly 4000 paediatric cardiac surgical patients analysed three protocols used over a six-year period.<sup>37</sup> They all received a preoperative dose of cefazolin 50 mg / kg. Patients in Group 1 continued to receive cefazolin for as long as the chest drains or central venous catheters were present. Group 2 had antibiotics discontinued after 48 hours, regardless of the presence of chest drains or central venous catheters. Group 3 had cefazolin continued until the chest drains were removed, irrespective of the presence

of a central line. This review showed a significantly reduced incidence of SWI in the Group 3 ( $p < 0.05$ ). The reviewers included both superficial incisional, deep incisional as well as mediastinitis / organ space infections, with an incidence of total SWI of up to 6.6 % in Group 2, compared with an incidence of 1.7 % in Group 3. Of these infections, 29 % were diagnosed after discharge from hospital.

Another retrospective study was performed to determine whether a decrease in the duration of prophylaxis causes an increase in the nosocomial infection rate.<sup>38</sup> 194 patients up to the age of 14 were included. They found that the prolongation of prophylaxis for longer than 48 hours increased the nosocomial infection rate. Also, limited prophylaxis to the first 48 hours after surgery did not increase the infection rate. 78.5 % of the patients received a cephalosporin in combination with an aminoglycoside. They included all sources of nosocomial sepsis, not limiting the study to SWI.

As cefazolin is a time-dependent antibiotic, total time above MIC is the key to its successful bactericidal action.<sup>6</sup> Continuous infusions of beta-lactam antibiotics have been shown to be more effective than intermittent dosing in animal studies.<sup>7</sup> A prospective, randomised pilot study conducted in 137 adults undergoing coronary artery bypass grafting looked at three groups of dosing regimens.<sup>39</sup> Group 1 received cefazolin 1 g at induction and at end of CPB. Group 2 received 2 g at induction, followed by an infusion of cefazolin at 20 mg / min throughout the surgery. Group 3 received 3 g of cefazolin before surgery commenced, followed by a lower infusion rate of 15 mg / min throughout surgery. Serum cefazolin levels were consistently higher, at all time points in Group 3 ( $p < 0.02$ ). At four of the six time points, Group 2 had higher levels than Group 1 ( $p < 0.04$ ). This study was underpowered to show a difference in outcome or incidence of SWI. There was no incidence of toxicity or adverse events as a result of these higher-than-normal doses.

A prospective study investigated perioperative serum levels of cefazolin in 19 children weighing less than 10 kg undergoing cardiac surgery.<sup>40</sup> The children received both cefazolin (40 mg / kg) and gentamicin (2 mg / kg) at induction, followed by a cefazolin dose of 35 mg / kg every eight hours, and a gentamicin dose

of 2 mg / kg every twelve hours, for 48 hours. This study showed levels over the MIC for potential pathogens (8 mcg / mL) throughout the surgery. At skin closure, some cefazolin levels were as low as 17 mcg / mL. This study showed decreasing serum levels during the CPB period of about 28 %, over an average of 72 minutes of CPB duration. This is in contrast to the work by Miller *et al.*, which suggested that the levels should plateau or increasing during CPB due to reduced renal clearance and altered protein binding.<sup>14</sup> Although this study quoted levels above MIC as adequate, some microbiologists are suggesting that four times MIC is a better target for effecting 100 % bactericidal action.<sup>7</sup>

An earlier study assessing serum levels of cefazolin during CPB used a smaller dose of 20 mg / kg (paediatric patients) and 1 g (adult patients), given intramuscularly, an hour prior to induction of anaesthesia.<sup>41</sup> This study involved 10 adults and 10 paediatric patients (7.2 to 28 kg body weight). In the paediatric group, the mean serum level was 20 mcg / mL during CPB. The study also demonstrated a drop in mean levels after initiation of CPB. Although the study protocol specified levels would be measured during sternal closure, there is no specific mention of these results. The lowest serum level recorded was 9.8 mcg / mL, well below the currently suggested four times MIC. No reference was made regarding target serum levels.

#### **4. The need for further research**

Paediatric data in the field of antimicrobial prophylaxis in cardiac surgery is mostly limited to retrospective studies, and small sample sizes. The altered pharmacokinetics and pharmacodynamics within the paediatric population is vastly different to that of adults, and extrapolation of adult data is not always appropriate.

Further research needs to be done in order to determine the most suitable antimicrobial prophylaxis regimen for paediatric patients. The timing of the intraoperative doses, as well as the addition of a dose to the priming volume of the CPB should be investigated by means of a large prospective randomised study involving a range of paediatric age groups.

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## **Part C: Manuscript**

## Cover letter



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15 March 2013

Dear Editor-in-Chief

**Cefazolin plasma concentrations in children less than 25 kilograms undergoing elective cardiac surgery: An audit of current clinical practice at Red Cross War Memorial Children's Hospital**

Attached please find our submission for publication in the Journal of Cardiothoracic and Vascular Anesthesia. This is original research, undertaken at the Red Cross War Memorial Children's Hospital in Cape Town, South Africa.

All the authors agree with, and are responsible for the data presented.

There are no conflicts of interests to declare.

Yours sincerely

Dr Alexandra Dresner, MBChB, FRCA

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"Our Mission is to be an outstanding teaching and research university, educating for life and addressing the challenges"

## **Title page**

### **Cefazolin plasma concentrations in children less than 25 kilograms undergoing elective cardiac surgery: An audit of current clinical practice at Red Cross War Memorial Children's Hospital**

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## Structured Abstract

Objectives: To determine the plasma concentrations of cefazolin during paediatric cardiac surgery involving cardiopulmonary bypass, using our current antibiotic prophylactic regimens. The minimum inhibitory concentration of cefazolin for sensitive *Staphylococcus* spp. is 8 mcg / mL. Our primary endpoint was to measure total intraoperative time spent above four times the minimum inhibitory concentration (32 mcg / mL).

Design: A non-interventional, prospective, observational study of current clinical practice

Setting: A specialist paediatric teaching hospital

Participants: 22 children with a body weight of less than 25 kilograms, undergoing elective cardiac surgery

Interventions: Patients received standard antibiotic prophylaxis of cefazolin 50 mg / kg after induction of anaesthesia, and then further doses as per the anaesthesiologist's normal practice. Seven subjects received an additional dose to the priming volume of the cardiopulmonary bypass pump. Eight subjects received an additional dose after four hours during cardiopulmonary bypass. Blood samples were taken at pre-determined time-points.

Measurements and main results: The plasma concentrations of cefazolin were measured by liquid chromatography. In all 22 patients, the plasma levels remained above 32mcg / mL for the entire duration of surgery. In the group who received the dose to the priming volume (n = 7), the levels were higher at sternal closure (p = 0.04).

Conclusion: Our current antibiotic regimen ensures plasma levels above the target of four times the minimum inhibitory concentration for the duration of surgery. The addition of a dose to the priming volume of the bypass pump results in higher levels at sternal closure.

**Key words**

Cefazolin; paediatric cardiac surgery; cardiopulmonary bypass; pharmacokinetics; sternal wound infections; antibiotic prophylaxis

## **Main text**

### **Introduction**

Postoperative sternal wound infection (SWI) is a considerable cause of morbidity and mortality in children following cardiac surgery for congenital heart disease. The incidence of SWI in the paediatric population ranges between 0.2 % and 4.8 %.<sup>1,2,3</sup> Deep SWI (mediastinitis) is associated with a prolonged hospital stay, additional operations, increased economic and emotional burden, as well as a mortality of up to 16 %.<sup>4</sup>

Prevention of SWI is a vital focus of all paediatric cardiac surgery units. As equivalent international guidelines do not exist for the paediatric population, adaptation of the available guidelines for adult cardiac patients is suggested.<sup>5</sup> Emphasis has been placed on appropriate antimicrobial prophylaxis, with three of the six Surgical Care Improvement Project (SCIP) guidelines relate specifically to antibiotic prophylaxis. The SCIP was established in 2004 with a mission to 'reduce preventable surgical morbidity and mortality in 25 % by 2010'.

The National Surgical Infection Prevention Project (NSIPP), the Society of Thoracic Surgeons (STS) and the American College of Cardiology / American Heart Association (ACC / AHA) have published guidelines for antibiotic prophylaxis in adult cardiac surgery regarding antibiotic choice, dose and duration of surgery.<sup>6,7,8,9</sup> These adult guidelines recommend cefazolin (a first generation cephalosporin) or cefuroxime (a second generation cephalosporin) as the antibiotic of choice for

patients without an allergy to beta-lactams. The routine addition of vancomycin may be warranted in a centre with a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>6,10</sup>

Analysis of breakpoints is helpful in determining an appropriate antimicrobial regimen. A breakpoint is the level of MIC of an antimicrobial agent at which a bacterium is deemed either susceptible or resistant to an antibiotic being used. The most recent data on the pharmacokinetic and pharmacodynamic breakpoints of cefazolin for *Staphylococcus* spp. and *Enterobacteriaceae* spp. was published in January 2012.<sup>11</sup> If either the MIC of a particular strain or the MIC<sub>90</sub> of a group strain is found to be at or below this breakpoint, the organism(s) can be considered 'susceptible'. If it is above the breakpoint, it is deemed 'resistant'.<sup>12</sup> The MIC<sub>90</sub> is the MIC below which 90 % of a group of organisms will show inhibited growth. The MIC<sub>90</sub> for cefazolin for sensitive *Staphylococcus* spp. is 8 mcg / mL, for intermediately-sensitive *Staphylococcus* spp. it is 16 mcg / mL and for resistant *Staphylococcus* spp. 32 mcg / mL. The MIC<sub>90</sub> for sensitive *Enterobacteriaceae* spp. is 2 mcg / mL for intermediately-sensitive *Enterobacteriaceae* spp. 8 mcg / mL and for resistant *Enterobacteriaceae* spp 16 mcg / mL.

As intraoperative contamination can occur at any point during surgery, it has been suggested that the dosing regimen should aim for plasma levels over the MIC for 100 % of the surgical duration as well as for at least a few hours after closure of the skin incision.<sup>13</sup> Some data suggests that, in order to ensure maximal time-dependent killing and prevent the development of resistance, a serum concentration that is at least four times the MIC should be targeted.<sup>14</sup> In a study relating intraoperative

gentamicin levels and postoperative wound infections in colorectal surgical patients, the gentamicin plasma concentrations at time of skin closure was the strongest independent risk factor for infection.<sup>15</sup>

The main goal of this study was to evaluate our tertiary paediatric centre's current antibiotic prophylaxis regimens, and ensure the plasma concentrations remain above four times the MIC of the common pathogens throughout the intraoperative period.

## **Methods**

This is a non-interventional observational prospective study of 22 children undergoing elective cardiac surgery for congenital heart disease requiring cardiopulmonary bypass (CPB) at the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. Ethical approval was obtained from the University of Cape Town's Faculty of Health Science Human Research Ethics Committee (HREC Reference: 536 / 2011). Valid, informed, written consent was obtained on the day prior to surgery from the child's legal guardian.

All the children had a body weight of less than 25 kilograms. Patients were excluded from the study if the expected or actual CPB time was less than 30 minutes, there was a history of penicillin or cephalosporin allergy, pre-existing renal or hepatic dysfunction was present, exposure to any antimicrobial agent within the previous week had occurred, and / or there was a history of a recent infection.

Patients all received standard perioperative anaesthetic and surgical care, according to the current practice at RCWMCH. Regarding CPB, a Stöckert SIII Mast-Mounted Heart Lung Machine with a Stöckert Hemotherm<sup>®</sup> Heater-Cooler was used, with Medtronic<sup>®</sup> tubing (0.25 inch to 0.375 inch diameter depending on the weight of the child). St Thomas' Hospital No. 2 cardioplegic solution was used, cooled to 5 to 8 degrees centigrade. A loading dose of 20 mL / kg was administered, followed by 10 mL / kg every 20 minutes during CPB.

Following induction of general anaesthesia, an initial dose of cefazolin 50 mg / kg of body weight was administered as an intravenous infusion over 1 minute, via a peripheral intravenous line. A further dose of cefazolin 50 mg / kg was given four to six hours after the initial dose. Depending on the duration of surgery, this may have occurred during CPB or postoperatively on the intensive care unit (ICU). Two of the cardiac anaesthesiologists at our institution routinely add a further dose of cefazolin (50 mg / kg) to the priming volume of the CPB circuit. The administration of this priming volume dose was documented and these children were analysed in two separate groups.

Blood samples were taken from the intra-arterial catheter placed in either the femoral or radial artery after induction of anaesthesia. Most similar studies have used arterial samples, as this avoids any possible contamination of the sample by the venous administration of the dose.<sup>16,17,18</sup> During CPB, the blood sample was taken from the CPB circuit. Each blood sample volume was 0.5 mL. A maximum of 16 samples was taken from each child (8 mL of blood).

In order to perform future pharmacokinetic studies of the effects of CPB on cefazolin plasma concentrations, a control population was required. In the group of children who had not had their maximum number of samples taken during surgery, further samples were taken postoperatively, following the dose given in ICU. This was done to reduce the variables, which contribute to pharmacokinetic differences between individuals as well as to help to determine the potential effects of the CPB.

Blood samples were taken at the following time-points (see Figure 1)

1. A baseline level (prior to administration of cefazolin)
2. Three minutes after completion of the initial dose infusion
3. Sternal incision
4. Cannulation of the aorta
5. Initiation of full-flow CPB
6. Every 30 to 60 minutes during CPB
7. Prior to the administration of a second dose, if given during CPB
8. Three minutes after administration of the second dose, if given during CPB
9. Immediately prior to termination of CPB
10. 10 to 15 minutes after termination of CPB
11. Sternal closure (if previous sample taken longer than 10 minutes before sternal closure, otherwise just the actual time of sternal closure was recorded)
12. Trough level prior to the second dose, if given on the ICU
13. Three minutes after administration of the second dose, if given on the ICU
14. One to two hours after the second dose in ICU
15. Three to four hours after the second dose in ICU

If the estimated CPB time was greater than 120 minutes, samples were taken every 60 minutes during CPB.

The samples were stored on ice for a maximum of six hours and then centrifuged for ten minutes at a relative centrifugal force of 1 500 g. The plasma was then stored at minus 70 degrees centigrade.

Plasma concentrations of cefazolin were determined using liquid chromatography tandem mass spectrometry. Sample preparation was achieved by protein precipitation with acetonitrile containing deuterated nevirapine as the internal standard. Chromatographic separation was performed on a Luna C18 5 $\mu$  column (Phenomenex<sup>®</sup>) with a mobile phase consisting of acetonitrile and water containing 0.1 % formic acid (25:75, v / v) delivered at a constant flow rate of 275 mL / min. An AB Sciex<sup>®</sup> API 4000 mass spectrometer was operated at unit resolution in the multiple-reaction-monitoring mode, monitoring the transition of the protonated molecular ion m / z 454.9 to the product ions at m / z 232.0 for cefazolin, and the protonated molecular ion m / z 270.1 to the product ions m / z 229.1 for the internal standard.

The assay was developed and validated for the determination of cefazolin from 20 mL human plasma over the concentration range of 0.586 – 110 mcg / mL. The within-day and between-day precision (coefficients of variation) was below 9 % for all quality control levels during the validation, and below 8 % during patient sample analysis.

If not directly measured, prediction of the concentration at the time of sternal closure was done using Microsoft Excel<sup>®</sup>. The data were first visually inspected to ascertain that the pharmacokinetic profile was in the log-linear elimination phase around the times of sternal incision and closure, and then a linear interpolation on the log-transformed data was used to predict the concentration.

Statistical analysis was done using Stata<sup>®</sup> data analysis and statistical software. A histogram was used for each variable to test for normality, revealing mostly skewed data. When two groups were compared, the non-parametric Mann-Whitney U test was applied. A p-value of less than 0.05 was considered to be statistically significant.

## **Results**

The demographic data for the 22 subjects is presented in Table 1 and the types of operations performed are depicted in Table 2. All 22 children fulfilled the inclusion and exclusion criteria. Two additional cases were enrolled into the study. One case was withdrawn due to an unexpectedly short CPB time of 13 minutes. The other subject was given antibiotics for a concurrent infection on the day prior to surgery.

In 19 of the subjects, a plasma concentration at the time of sternal closure was calculated from the log-linear elimination phase study. An actual sample was not taken in these cases because the sternal closure was performed very soon after termination of CPB, and a sample had already been taken within ten minutes of sternal closure.

All of the patients, regardless of intraoperative re-dosing or the addition of a dose in the priming volume of the pump, had 100 % of the measured and calculated plasma concentrations over 32 mcg / mL for the duration of surgery. This represents the target concentration of four times the MIC for sensitive *Staphylococcus* spp. This is also well above four times the MIC for the sensitive *Enterobacteriaceae* spp. (8 mcg / mL). (Figure 2)

All of the subjects received the initial dose of cefazolin within 30 to 60 minutes of skin incision, which is in keeping with the international adult guidelines.<sup>6,7,8,9</sup>

Seven patients (31.8 %) received a dose of cefazolin to the priming volume of the pump (Group 1) and fifteen patients (69.2 %) did not receive a dose to the priming volume (Group 2). In Group 1, six patients received an additional dose of cefazolin during CPB (four hours after the initial dose). In Group 2, only two patients received an additional dose during surgery. Both the CPB duration, and total operating time were significantly longer in Group 1 ( $p = 0.001$ ) (see Table 3). The median plasma concentrations at sternal closure were higher in Group 1 compared to Group 2 (113 mcg / mL vs. 64 mcg / mL,  $p = 0.04$ ), although both were above the target of 32 mcg / mL. (Figure 3)

In those patients who had a total CPB time of less than 120 minutes ( $n = 11$ ), the plasma concentration of cefazolin was significantly lower at sternal closure, compared to those with longer CPB times (64 mcg / mL vs. 113 mcg / mL,  $p = 0.04$ ). Of the group with a longer CPB group, 6 of the 11 subjects received a dose to the priming volume of the pump as well as an additional dose during CPB. In the group with a shorter CPB time, only 1 subject received an additional dose during CPB.

In subjects where the lowest recorded temperature was below 30 degrees centigrade (n = 11), the plasma levels at sternal closure were significantly higher (p = 0.02). In this lower temperature group, six of the eleven children received a dose to the priming volume.

Three patients developed sternal wound infections (13 %). One of these cultured MRSA in a pus swab, while the other two were culture-negative. Two of the 22 patients died postoperatively: one died from non-infective cardiac causes, while another died from mediastinitis secondary to MRSA, twelve days postoperatively.

## **Discussion**

Cardiopulmonary bypass can affect the pharmacokinetics and pharmacodynamics of drugs for a variety of reasons. The main factors are an increased volume of distribution (with resultant haemodilution), altered protein binding, decreased elimination, reduced organ perfusion and hypothermia.<sup>19</sup> With prolonged CPB duration and the lower core body temperatures that occur during the process, these effects will be exaggerated. In order to maintain plasma levels for the duration of surgery, many cardiac anaesthesiologists prime the CPB pump with cefazolin and give additional doses intraoperatively. The correct dose, and regimen required to maintain these levels in the paediatric population are still under debate, as is the duration of perioperative prophylaxis.<sup>10</sup> Plasma concentrations of at least four times the MIC for susceptible bacteria should be maintained for the intraoperative period, as this is when bacterial contamination is the greatest risk.<sup>13</sup>

The first dose should be given within 30 to 60 minutes before surgical incision. The NSIPP recommends repeated intraoperative doses if the operation is still in progress after two half-lives following the first dose, while the National Institute for Health and Clinical Excellence (NICE) suggests re-dosing in surgical procedures lasting longer than the half-life of the antibiotic used.<sup>20</sup> The STS recommends a second dose every three to four hours during surgery.<sup>7</sup> A total duration of postoperative prophylaxis of less than 48 hours is suggested. Higher doses and prolonged duration of administration of antibiotics is associated with higher medical costs and the development of antimicrobial resistance.<sup>21</sup> The only published cases of possible cefazolin toxicity suggested that high cerebrospinal fluid concentrations (CSF) of cefazolin (34 – 106 mcg / mL) were associated with seizures in three adult patients.<sup>22</sup> No reference range exists for CSF cefazolin concentrations, and the correlated serum levels were 360 – 1000 mcg / mL. The highest plasma level in our study was a peak level of 722 mcg / mL following a second dose during CPB. This might hold clinical relevance, as seizure activity will be masked by general anaesthesia.

The usual serum half-life of cefazolin is 108 minutes (1.8 hours).<sup>23</sup> This can be prolonged during CPB owing to reduced renal clearance and increased total body distribution.<sup>24</sup> Most antibiotic prophylaxis guidelines recommend re-dosing at three to four hour intervals. In a retrospective study of over 1500 patients undergoing cardiac surgery lasting longer than 240 minutes, the overall risk of SWI was similar in those patients who received additional intraoperative doses and those who did not. However, there was a clinical benefit in procedures lasting longer than 400 minutes.

Overall, the authors calculated a potential 16 % reduction in risk of SWI if a strategy of re-dosing in all procedures lasting than 240 minutes was employed.<sup>25</sup>

The effect of hypothermia on serum cefazolin levels was investigated in a prospective study by Caffarelli *et al.*<sup>26</sup> This study found that serum cefazolin levels were not affected by a CPB duration of less than 120 minutes with mild to moderate hypothermia. In cases requiring CPB times of longer than 120 minutes, the plasma levels dropped to ineffective therapeutic levels in 50 % of patients. Profound hypothermic circulatory arrest appeared to have a slightly protective effect on the serum levels. Although these cases also had prolonged CPB times, only 10 % of patients had a sub-therapeutic plasma level. This is possibly due to the delayed renal excretion that can occur at low body temperatures.

Although all subjects had plasma concentrations above 32 mcg / mL at sternal closure, the levels in Group 1 were higher. These children also had a longer duration of CPB and overall surgical time. The two clinicians, who routinely add a dose of cefazolin to the priming volume of the pump, are the more senior and experienced paediatric cardiac anaesthesiologists at RCWMCH. These cases may have been allocated to them as they were the more challenging cases, with an expected prolonged CPB time. Six of the seven cases in this group also received an additional dose during CPB, four hours after the initial dose. The increased plasma levels at sternal closure were therefore due to a combination of the priming dose and the additional dose during CPB. As only two of the fifteen cases in Group 2 received an additional dose of cefazolin during CPB, a statistically significant comparison is not possible.

There are a few notable limitations to this study. Due to the small sample size, the study was underpowered to comment on the efficacy of the antibiotic prophylaxis. We also failed to reach statistical significance with most comparisons. There are no clear MIC targets for antibiotic prophylaxis, as most studies are specifically aimed at therapeutic goals. We chose the upper limit of suggested targets from recent literature, of four times MIC for 100 % of the surgical time, but other similar studies have aimed at levels over MIC for 40 to 50 % of the time.<sup>12,13</sup>

As this was a non-interventional, observational study, there was no randomisation of patients. In some cases, a dose of cefazolin was added to the priming volume, and further intraoperative administration was left to the responsible anaesthesiologist. This led to unequal group distribution.

The total cefazolin plasma concentration was measured in this study. As it is the free fraction that is available to bind at the bacterial cell membrane, any alterations in the protein binding will also affect this level. This is not taken into account in this study.

To determine the effects of CPB on the plasma concentrations, further pharmacokinetic analysis of the data is planned. Most of the subjects had blood samples taken postoperatively on ICU, which will then serve as a control for this further work.

In conclusion, the current antibiotic prophylaxis regimen at our institution provides consistently adequate plasma concentrations of cefazolin. The addition of an

additional dose to the priming volume of the pump, and intraoperative re-dosing in cases that have a longer duration of CPB, result in higher plasma levels at the time of sternal closure.

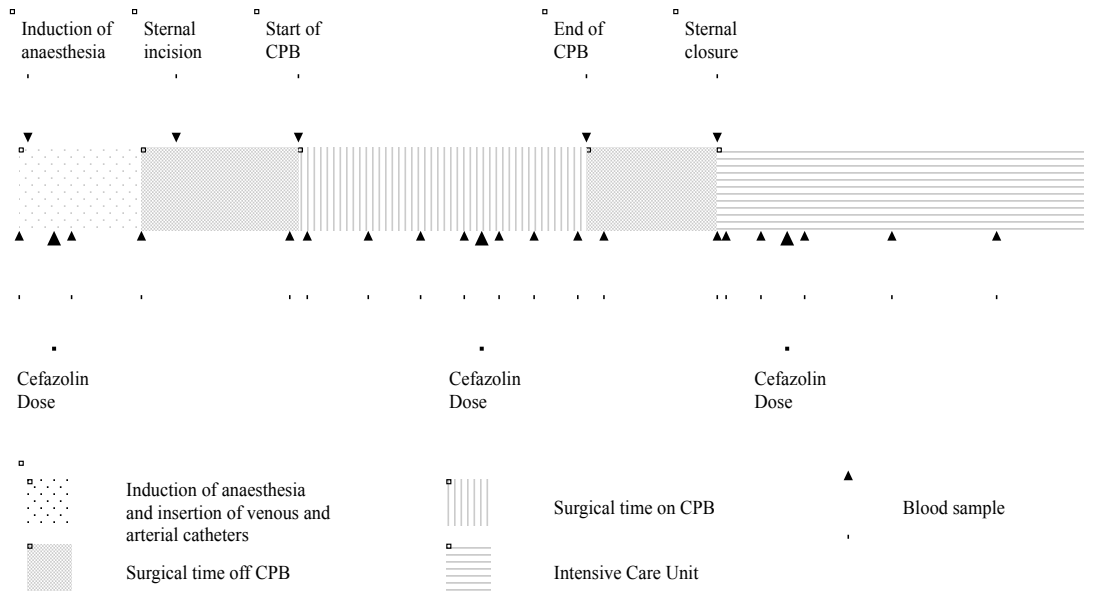
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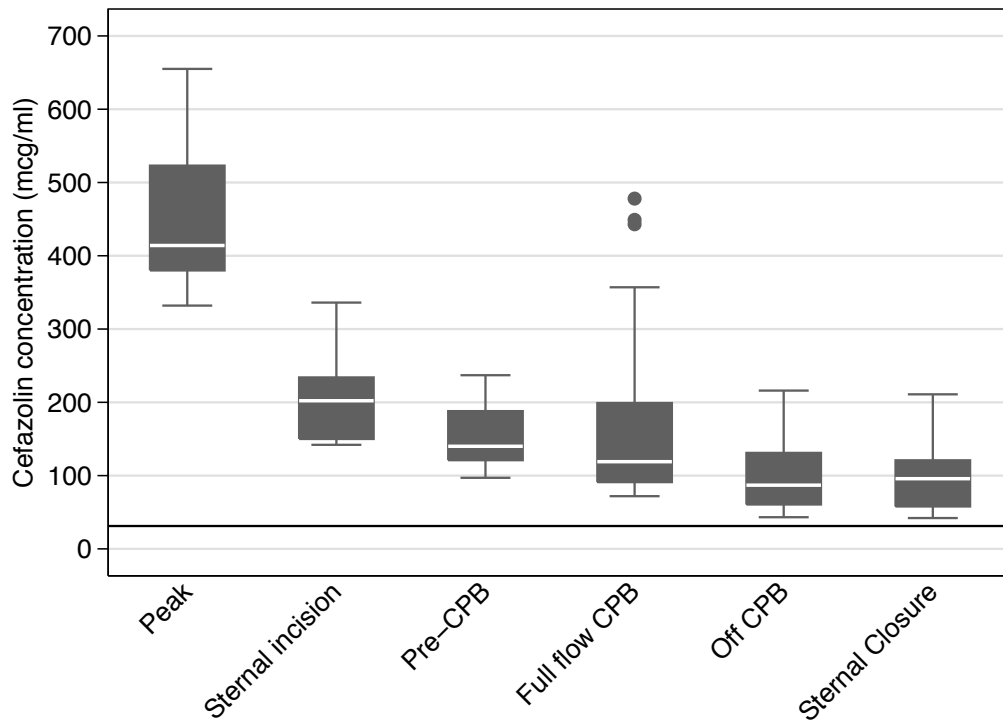
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**Figure 1: Timeline showing antibiotic dosing and blood sampling times**

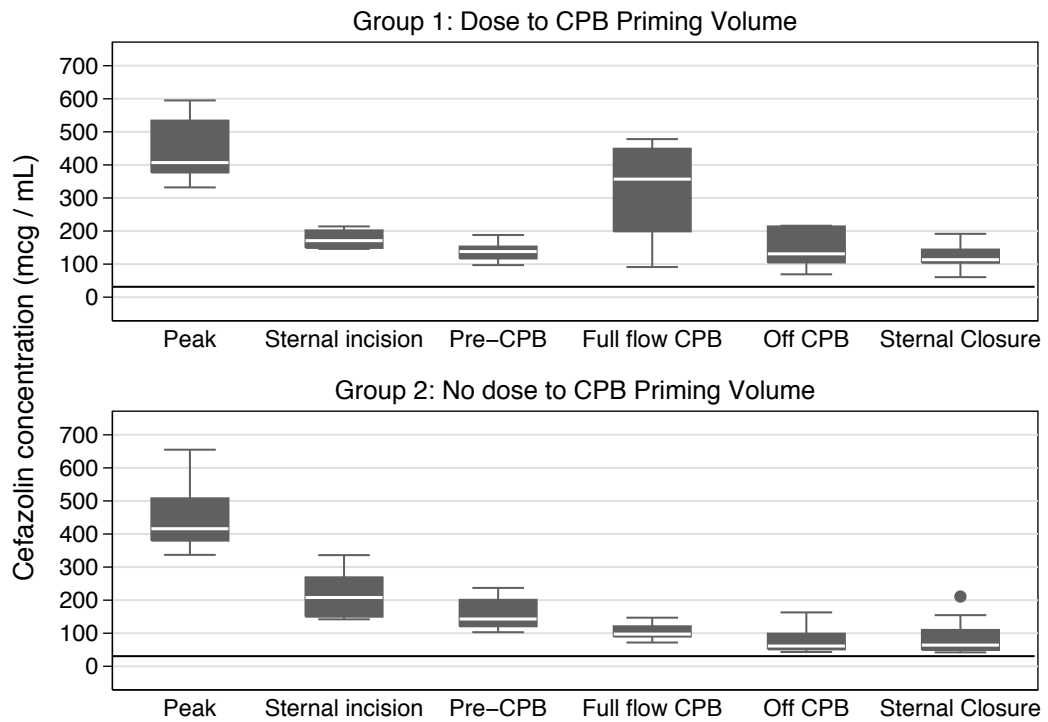


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**Figure 2: Box plot showing plasma concentrations of cefazolin at intraoperative time-points (Bold horizontal line represents 32 mcg / mL, four times MIC for *Staphylococcus* spp.) (n=22)**



**Figure 3: Box plots showing the difference in plasma concentrations of cefazolin between Group 1 (n = 7) and Group 2 (n = 15) (Bold horizontal line represents 32 mcg / mL, four times MIC for *Staphylococcus* spp.)**



**Table 1: Demographic and intraoperative data of patients (n=22)**

	Median (p50)	Interquartile range (p25 – p75)	Minimum value	Maximum value
Age (months)	19.5	11.0 – 46.0	1.0	94
Weight (kg)	8.7	6.0 – 12.5	2.0	21.6
Height (cm)	77.5	70.0 – 93.0	45.0	117.0
Lowest temperature on CPB (°C)	30.4	25.1 – 32.2	20.0	35.7
CPB priming volume (ml / kg)	41.9	33.4 – 64.4	16.2	225.0
Cardioplegia used (ml / kg)	48.9	35.2 – 90.1	10.7	350.0
Duration of surgery (mins)	165	139 – 337	83	400
CPB time (mins)	115	79 – 242	35	336

**Table 2: Type of cardiac surgery performed (n = 22)**

Surgery performed	Number of cases (n = 22)
Repair of ventricular septal defect	5
Repair of transposition of the great arteries	4
Repair of atrioventricular septal defect	3
Repair of pulmonary atresia	2
Repair of Tetralogy of Fallot	2
Augmentation of right ventricular outflow tract	2
Repair of atrial septal defect	1
Ross Procedure for aortic regurgitation	1
Repair of total anomalous pulmonary venous drainage	1
Repair of partial anomalous pulmonary venous drainage	1

**Table 3: Comparison of Group 1 (dose to priming volume) vs. Group 2 (no dose to priming volume)**

		Median (p50)	Interquartile range (p25 – p75)
Group 1 (n = 7)	CPB time (mins)	270	165 – 275
	Total surgical time (mins)	352	230 – 382
	Plasma concentration at sternal closure (mcg / mL)	113	104 – 144
Group 2 (n = 15)	CPB time (mins)	81	72 – 125
	Total surgical time (mins)	150	129 – 172
	Plasma concentration at sternal closure (mcg / mL)	64	49 – 110

## **Part D: Supporting documents**

**Data collection form**

Patient No: \_\_\_\_\_

Date of surgery: \_\_\_\_\_

Primary cardiac diagnosis: \_\_\_\_\_

Operation performed: \_\_\_\_\_

Age: \_\_\_\_\_

Gender: \_\_\_\_\_

Weight (kg): \_\_\_\_\_

Ethnic group: \_\_\_\_\_

Height (cm): \_\_\_\_\_

Cefazolin dose (50 mg / kg): \_\_\_\_\_

Co-morbid conditions: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Current medication: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Allergies: \_\_\_\_\_

Any antibiotics in past week? \_\_\_\_\_

Any recent illness/infection? \_\_\_\_\_

## Preoperative biochemistry

Hb: \_\_\_\_\_

Hkt: \_\_\_\_\_

WCC: \_\_\_\_\_

Plt: \_\_\_\_\_

Na: \_\_\_\_\_

K: \_\_\_\_\_

Urea: \_\_\_\_\_

Creat: \_\_\_\_\_

Estimated GFR (Schwartz formula) (mL/min/1.73m<sup>2</sup>) = \_\_\_\_\_

$[k \times \text{height (cm)}] / [\text{Serum creatinine (mmol/l)}] * 88.402$

*Children < 1 year of age: Preterm baby k=0.33, Fullterm baby k=0.45*

*1-12 years of age: k = 0.55*

Peripheral IV cannula: \_\_\_\_\_

Central venous catheter: \_\_\_\_\_

Intra-arterial catheter: \_\_\_\_\_

Any evidence of sternal infection in first 2 weeks post operatively? (Y/N) \_\_\_\_\_

If yes, details of infection and treatment:

\_\_\_\_\_  
\_\_\_\_\_

### Times and Events

Event	Time	Sample	Further doses and time
Induction of anaesthesia			
Baseline sample		00	
Dose 1			
Peak (3 mins)		01	
Sternal incision		02	
Pre-CPB (aortic cannulation)		03	
Full Flow CPB		04	
CPB		05	
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
CPB			
Off CPB			
Sternal Closure			
CPB residual		UF	Volume:
Trough level			
Dose (ICU)			
Sample 1			
Sample 2			
Sample 3			

Dose given to CPB priming? (Y/N) \_\_\_\_\_

Type of cardioplegia used: \_\_\_\_\_

Total volume of cardioplegia used: \_\_\_\_\_

Total CPB time (mins): \_\_\_\_\_

Total AXC time (mins): \_\_\_\_\_

**Fluid given during surgery**

<b>Crystalloid</b>	<b>Type of fluid</b>	<b>Volume</b>
Pre-CPB:	_____	_____
During CPB:	_____	_____
Post-CPB:	_____	_____

<b>Colloid</b>	<b>Type of fluid</b>	<b>Volume</b>
Pre-CPB:	_____	_____
During CPB:	_____	_____
Post-CPB:	_____	_____

<b>Blood products</b>	<b>Type of fluid</b>	<b>Volume</b>
Pre-CPB:	_____	_____
During CPB:	_____	_____
Post-CPB:	_____	_____

Priming fluid and volume CPB: \_\_\_\_\_

Total urine output: \_\_\_\_\_

**Perioperative Biochemistry**

<b>Time:</b>												
pH												
BE												
HCO <sub>3</sub>												
Lactate												
Hb												
Hkt												



## **Parent Information Sheet**

Your child is requiring open-heart surgery. During the surgery your child will require a heart bypass machine. This machine does the work of the heart and lungs while the surgeons are operating on the heart. Blood circulates through the machine and then back into the child's body.

We routinely give a dose of antibiotics at the start of the operation to prevent any infection in the wound afterwards. We want to make sure that the levels of antibiotics in the blood remain adequate for the duration of surgery. There is not much available literature regarding these levels in children.

This will involve taking blood samples during surgery and measuring the levels of antibiotics. The blood will be taken from a special catheter in the artery, which is routinely placed while the child is sleeping before the surgery starts. A maximum of 16 samples will be taken during the surgery, which will be less than 10ml in total of blood (equivalent of two teaspoons). This will not affect your child's recovery from surgery.

There will be no direct benefit to the children who participate in the study.

Participating in the study will not affect your child's care in any way. Once you have given consent to your child being included in the study, you may withdraw consent at any time and this will also not affect your child's care.

The results from this study can help us to ensure we are giving the correct dose of antibiotics. The appropriate Ethics Committee has approved this study.

If you require any further information please feel free to contact me.

Chief Researcher:

Dr Alex Dresner

Anaesthetic Registrar

Tel: 079 211 6580

## CONSENT TO INCLUSION OF CHILD IN CEFAZOLIN STUDY

*Affix hospital sticker here (if available)*

Name of patient: \_\_\_\_\_

Hospital no.: \_\_\_\_\_

Date of birth: \_\_\_\_\_

I \_\_\_\_\_ (parent/guardian) hereby consent to the inclusion of my child \_\_\_\_\_ (child's name) in the cefazolin plasma concentrations study in cardiac surgery.

I have received written information on the study. Yes  No

The study has been fully explained to me. Yes  No

I have had my questions answered adequately. Yes  No

I give permission for my child's blood samples to be stored and analysed at a later date Yes  No

I have the right to withdraw consent at any time and my child's management will not be compromised in any way.

Full name of parent/guardian: \_\_\_\_\_

Relationship to child: \_\_\_\_\_

Signature of parent/guardian: \_\_\_\_\_

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

Full name of witness: \_\_\_\_\_

Signature of witness: \_\_\_\_\_

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

## **Inligtingstuk vir ouers**

U kind benodig ope-hart chirurgie. Tydens die prosedure sal u kind 'n hart omleidingsmasjien benodig. Die masjien doen die werk van die hart en longe terwyl die chirurg op die hart opereer. Bloed sirkuleer deur die masjien en dan terug na die kind se liggaam.

Ons gee roetneweg 'n dosis antibiotika aan die begin van die operasie om infeksie in die wond na die tyd te voorkom. Ons wil seker maak dat die antibiotika se vlakke in die bloed voldoende bly vir die volle durasie van die chirurgie. Daar is nie baie inligting aangaande hierdie vlakke in kinders beskikbaar nie.

Dit behels dat daar gedurende die operasie bloedmonsters geneem sal word om die vlak van die antibiotika te toets. Die bloed sal uit 'n spesiale kateter in 'n aar geneem word. Hierdie kateter word roetneweg ingeplaas voor die chirurgie begin, maar na die kind reeds slaap. 'n Maksimum van 16 monsters sal gedurende die chirurgie geneem word. Die totale volume is minder as 10ml bloed (gelykstaande aan twee teelepels). Dit sal nie u kind se herstel na die chirurgie beïnvloed nie.

Daar sal geen direkte voordeel wees vir kinders wat aan hierdie studie deelneem nie.

Deelname aan die studie sal nie die sorg wat u kind kry op enige manier beïnvloed nie. Nadat u toestemming gegee het vir deelname aan die studie, mag u toestemming onttrek op enige stadium. Dit sal ook nie die sorg wat u kind kry op enige manier beïnvloed nie.

Die uitslae van die studies sal ons help om te verseker dat die korrekte dosis antibiotika gegee word. Die toepaslike Etiekkomitee het hierdie studie goedgekeur.

Indien u verdere inligting benodig, is u welkom om my te kontak.

Hoofnavorser :

Dr Alex Dresner (Kliniese Assistent in Narkose)

Tel: 079 211 6580

## TOESTEMMINGSVORM VIR INSLUITING VAN KIND BY CEFAZOLIN STUDIE

*Plak hospitaalplakker hier (indien beskikbaar)*

Naam van pasiënt: \_\_\_\_\_

Hospitaalnr.: \_\_\_\_\_

Geboortedatum: \_\_\_\_\_

Ek \_\_\_\_\_ (ouer/voog) gee hiermee my toestemming tot die insluiting van my kind \_\_\_\_\_ (kind se naam) in die cefazolin-plasmakonsentrasie studie tydens hartchirurgie.

Ek het geskrewe inligting oor die studie ontvang. Ja  Nee

Die studie is volledig aan my verduidelik. Ja  Nee

My vrae is voldoende beantwoord. Ja  Nee

Ek gee toestemming dat my kind se bloedmonsters gestoor mag word en by 'n latere geleentheid geanaliseer mag word. Ja  Nee

Ek het die reg om toestemming op enige stadium te onttrek sonder dat my kind se behandeling op enige manier benadeel sal word.

Volle naam van ouer/voog: \_\_\_\_\_

Verhouding tot kind: \_\_\_\_\_

Handtekening van ouer/voog: \_\_\_\_\_

Datum: \_\_\_\_\_

Volle naam van getuie: \_\_\_\_\_

Handtekening van getuie: \_\_\_\_\_

Datum: \_\_\_\_\_

## **Iphepha lengcaciso eya kubazali**

Umntwana wakho kuya kufuneka enziwe utyando entliziyweni. Ngexesha lotyando kuza kufuneka umntwana wakho abe nomatshini wotyando lwentliziyo othintela igazi lingagqithi kule ndawo inengxaki xa liphuma emzimbeni (ibypass machine). Lo matshini wenza umsebenzi wentliziyo nowemiphunga ngeli xesha esenza utyando entliziyweni ugqirha. IGazi lijikeleza kulo matshini ze liphinde libuyele emzimbeni womntwana.

Ngokommiselo sisinika umlinganiselo othile wesibulala-zintsholongwane isigulane ngaphambi kokuqalisa utyando, ukuthintela ukusuleleka kwenxeba ziintsholongwane emva kotyando. Sifuna ukuqinisekisa ukuba ubungakanani besibulala zintsholongwane egazini uhlala ungothanelekileyo de lugqitywe utyando.

Oku kubandakanya nokutsalwa kweesampulu zegazi ngexesha lotyando nokujongwa kobungakanani besibulala-zintsholongwane. Igazi elo liye litsalwe ngekhathetha kumthambo ongunothumela (i-athari), eye ithi ngokommiselo ifakwe emntwaneni ngexesha aleleyo ngaphambi kokuqaliswa kotyando. Umlinganiselo ongowona uphezulu weesampulu ezili-16 zegazi ziya kutsalwa xa kutyandwa, kodwa loo mlinganiselo uya kuba ngaphantsi kwe-10ml uwonke (ulingane neetispuni ezimbini). Akukho nto iya kuphazamisana nokuchacha komntwana wakho emva kotyando.

Iziphumo zolu phando ziya kusinceda ukuqinisekisa ukuba sisineke umlinganiselo ochanekileyo wesibulala-zintsholongwane isigulane. IKomiti ejongene neeNkqubo eziseSikweni ikwamkele oku.

Ukuba ufuna iingcombolo ezithe vetshe unganditsalela ngokukhululekileyo.

IGosa loPhando eliyiNtloko:

Gqr Alex Dresner

IREjistra ye-Anesthetikhi

IFowuni: 079 211 6580

**IMVUMELWANO YOKUBANDAKANYWA  
KUPHANDO LWE- CEFAZOLIN**

**KOMNTWANA**

*Ncamathelisa isitika saseSibhedlele apha (ukuba sikhona)*

Igama lesigulane: \_\_\_\_\_

INomb. yefayili yaseSibhedlele: \_\_\_\_\_

Umhla wokuzalwa: \_\_\_\_\_

Mna \_\_\_\_\_ (umzali/umgcini-mntwana) ndinika imvume yokuba abandakanywe umntwana wam u \_\_\_\_\_ (igama lomntwana) kuphando olusebenzisa into ekuthiwa yi-cefazolin plasma xa kusenziwa utyando lwentliziyo.

Ndifumene imbalelwano endazisa ngolu phando.

Ewe  Hayi

Ndicaciselwe ngokupheleleyo ngolu phando.

Ewe  Hayi

Ndiphendulwe ngokwanelisayo kuyo yonke imibuzo ebendinayo.

Ewe  Hayi

Ndinikezela imvume yokuba elinye igazi lomntwana wam ligcinwe lijongisiswe ngelinye ixesha.

Ewe  Hayi

Ndinelungelo lokumrhoxisa nangaliphi ixesha umntwana wam kodwa oko kungayi kuyichaphazela inkqubo yokunyangwa kwakhe nangayiphi na indlela.

Igama elipheleleyo lomzali/lomondli: \_\_\_\_\_

Ulwalamano nomntwana: \_\_\_\_\_

Kutyikitya umzali/umondli: \_\_\_\_\_

Umhla: \_\_\_\_\_

Igama elipheleleyo lengqina: \_\_\_\_\_

Kutyikitya ingqina: \_\_\_\_\_

Umhla: \_\_\_\_\_

# Ethics approval letter



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

14 November 2011

HREC REF: 536/2011

Dr A Dresner,  
Anaesthetics  
D-23  
NGSH

Dear Dr Dresner,

**PROJECT TITLE: CEFAZOLIN PLASMA CONCENTRATIONS IN CHILDREN LESS THAN 15 KILOGRAMS UNDERGOING ELECTIVE CARDIAC SURGERY: AN AUDIT OF CURRENT CLINICAL PRACTICE AT RED CROSS WAR MEMORAL CHILDREN'S HOSPITAL**

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 15 November 2012**

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.

# Amendment to ethics approval



UNIVERSITY OF CAPE TOWN  
UNIVERSITEIT VAN KAPSTAD

FACULTY OF HEALTH SCIENCES  
Human Research Ethics Committee

## Amendment Form

Date	26/06/2012
HREC REF Number	HREC 536/2011
Protocol number (if applicable) & Protocol title	Cefazolin plasma concentrations in children less than 15 kilograms undergoing elective cardiac surgery: An audit of current clinical practice at Red Cross War Memorial Children's Hospital
Principal Investigator	Dr Alex Dresner
Department / Office Internal Mail Address	Dept of Anaesthesia, D23, Groote Schuur Hospital

## List of Proposed Amendments with Revised Version Numbers and Dates

1. Change protocol title to: Cefazolin plasma concentrations in children less than 25 kilograms undergoing elective cardiac surgery: An audit of current clinical practice at Red Cross War Memorial Children's Hospital
2. Inclusion Criteria: Children up to the body weight of 25kg (previously 15kg)
3. A second dose may be administered 3-4 hours after the induction dose, as per recent antibiotic prophylaxis guidelines.

RESEARCH ETHICS COMMITTEE

2012 -07- 27

HEALTH SCIENCES FACULTY  
UNIVERSITY OF CAPE TOWN

## HREC office use only (FWA00001637; IRB00001938)

<input checked="" type="checkbox"/> Approved	<input checked="" type="checkbox"/> Type of review: Expedited	<input type="checkbox"/> Full committee
This serves as notification that all changes and documentation described above are approved.		
Signature Chairperson of the HREC		Date 30/7/2012

## Notes for authors (from <http://www.jcardioanesthesia.com/authorinfo>)

### Journal of Cardiothoracic and Vascular Anesthesia

The *Journal of Cardiothoracic and Vascular Anesthesia* will consider for publication suitable articles on all topics related to anesthesia for cardiac, vascular, and thoracic surgery. The scope of this *Journal* is broad and seeks to consolidate all material pertinent to cardiothoracic anesthesiology, including topics from critical care medicine, pharmacology, monitoring, perfusion technology, internal medicine, surgery, and transplantation. Articles, editorials, letters to the Editor, and other text material in the *Journal* represent the opinion of the authors and do not necessarily reflect the opinion of the Editor, Editorial Board, or Publisher. The Editors and Publisher deny any responsibility or liability for statements and opinions expressed by the authors. Neither the Editor nor the Publisher guarantees, warrants, or endorses any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service. Authors submitting a manuscript do so with the understanding that if it is accepted for publication, copyright of the article, including the right to reproduce the article in all forms and media, shall be assigned exclusively to the Publisher. Following acceptance for publication, in order to comply with United States copyright law and the requirements of the insurance carrier, the Publisher will require authors of accepted manuscripts and letters to sign a copyright release form.

**SUBMISSION** All submissions must be directed to our web site: <http://ees.elsevier.com/jcva>. Offline submission is not permitted, unless requested by the Editorial Office. On the home page you will find links not only to this Guide, but also to a Tutorial for Authors, Artwork Guidelines, and general information on the *Journal*. First-time Corresponding Authors can register from the home page by clicking on the register link. You will receive e-mails guiding you on the basic information for submitting a manuscript. Each page of the web site during the review process contains important information for that step. **The Editorial Office will send by e-mail only to the Corresponding Author all communications related to the status of a submission, including the final decision and the scheduled date of**

**publication.** Detailed information on submissions is provided below. Further inquiries and information may be directed to the Editorial Office at: [dwalk@louisville.edu](mailto:dwalk@louisville.edu).

**EDITORIAL POLICIES** Manuscripts are accepted for consideration on the condition that they are contributed solely to the *Journal of Cardiothoracic and Vascular Anesthesia*. No substantial part of a paper may have been published elsewhere, except for a scientific abstract. Manuscripts will be reviewed by the Editor in Chief, Section Editors, members of the Editorial Board, and appropriate guest reviewers. Acceptance of a paper for publication is based on the originality and quality of the observation or investigation and the clarity of the presentation. Clinically relevant material is especially desirable. Good English usage is an essential prerequisite for consideration of the paper. In all cases the authors must accept the responsibility of conforming to the instructions in the sections below. Submissions must conform fully before reviewers will be assigned. Substantial non-conformity may result in outright rejection. If a submitted article is accepted for publication, editorial revisions may be made to aid clarity and understanding without altering the meaning.

**Electronic-only Publication.** Letters to the Editor, the Cardiac Calendar, and selected articles from other sections (e.g., Case Reports, Diagnostic Dilemmas, and E-Challenges) are published E-ONLY. Like print articles, E-only articles will be indexed in Medline and elsewhere and will be included on the print issue's Table of Contents.

**Experimentation subjects.** Papers reporting human experimentation will be reviewed in accordance with the precepts established by the Helsinki Declaration (available at <http://www.wma.net/en/30publications/10policies/b3/>). Such papers must include a statement that human investigations were performed after approval by a local Human Investigations Committee and after obtaining informed consent from a patient or other responsible individuals. All experimental work with animals must conform to American Physiological Society Guiding Principles for the Care and Use of Vertebrate Animals in Research and Training ([http://www.the-aps.org/pa/resources/policyStmnts/paPolicyStmnts\\_Guide.htm](http://www.the-aps.org/pa/resources/policyStmnts/paPolicyStmnts_Guide.htm)).

**Article types.** The following may be submitted: Original Research Articles, Case Reports, Review Articles, Emerging Technology Reviews, E-Challenges and Clinical Decisions, Case Conferences, Pro and Con Articles, Diagnostic Dilemmas, Special Articles (those not easily suited to another type), and Correspondence (letters to the Editor). Cardiac Anesthesia Fellows Education (CAFE) articles may be submitted by cardiac fellows and their mentors. The CAFE section is devoted to developing the clinical and publication skills of fellows. Articles for this section may be submitted as any of the above article types and may be augmented by expert commentaries. Case Conferences should be augmented by expert commentaries. Potential authors are invited to e-mail the Editorial Office to contact Editor in regard to interest in a proposed submission.

**DETAILS ON ARTICLE TYPES** For examples of all article types, see any recent issue of the *Journal*. For all submissions, each table, figure, or video/audio clip is to be included only as a separate Table, Figure, or Video/Audio Clip document, and is not to be placed in the Manuscript (main text) document. Video stills must be submitted as Figures.

**Original Research Articles.** This article type requires 4 documents: Cover Letter, Title Page, Structured Abstract, and Manuscript.

The **Structured Abstract** is limited to 250 words (including section headings). The abstract should consist of 7 paragraphs: 1. Objective(s): What scientific question was the study designed to answer? 2. Design: A phrase describing whether a study is prospective, randomized, blinded, retrospective, etc. 3. Setting: Type of hospital or laboratory; university or community setting; single or multi-institutional. 4. Participants: Patients, volunteers, animals. 5. Interventions: What interventions were done to the participants? 6. Measurements and Main Results: How was the outcome of the intervention(s) assessed? What were the major finding(s) of interest? 7. Conclusions: What conclusion(s) may be reasonably drawn from the results of the study? Following these 7 paragraphs, repeat the list of Key Words that you have uploaded onto the Key Word page. No references or abbreviations should be used in the abstract. The name or location of the authors institution should not be revealed.

The **Manuscript document** must have 4 identified sections: Introduction, Methods, Results, and Discussion. A description of the statistical methods used should be

included in the last part of the Methods section. The name or location of the authors' institution should not be revealed in this document.

**Case Reports.** This article type requires 4 documents: Cover Letter, Title Page, Summary, and Manuscript. The Manuscript document should begin with a short introduction to the clinical context of the case and follow with 2 identified sections: Case Report and Discussion. A 1-paragraph summary should complete the article. In most situations the introduction and final summary can be the basis for the Summary item.

**Case Conferences.** These articles are handled by a Section Editor for Case Conferences. Some offline communication between authors and editors may be required.

- A Case Conference comprises a Case Report with a Discussion and one or more experts commentaries that provide input from related specialties and/or viewpoint(s) on anesthetic or intensive care management of the case.
- A commentator needs to provide his or her full name, degrees, affiliation, and e-mail address. Commentators will be listed as authors.
- Figures, video clips, tables, and references from the case authors and commentators are desirable to expand the teaching value of the case. Follow the guidelines below for preparing figures, video clips, tables, and references.
- The final version of the Case Conference will have its references compiled into a single consecutively numbered list.

**Review Articles.** Review articles may be invited by a Section Editor, but invitation is not necessary for full consideration. This article type requires 3 documents: Cover Letter, Title Page, and Manuscript. The scope and purpose of the review must be clearly defined and accomplished in the Manuscript document. Authors are encouraged to provide relevant table, figure, and video clip documents.

**Diagnostic Dilemmas.** This cogent article type is in two parts. First, it presents a case with difficult diagnosis, usually resulting from preliminary graphic evidence. The reader is then invited to project a tentative diagnosis. In the second part, the

interpretation of further imaging techniques or other investigation is provided to resolve the dilemma. High quality figures and/or video clips are vital for these submissions.

**Letters to the Editor.** A Cover Letter and a Title Page are needed separate from the Letter (Manuscript) item. The Letter to the Editor should be double-spaced, brief, and concisely focused. Cited works must have full, accurate references. Figures, video clips, and tables may be included. Letters to the Editor will be published only online.

### **MANUSCRIPT DETAILS**

- All documents (except figures) should be prepared in Microsoft Word for Windows or a fully compatible program, not in .pdf or any graphic format.
- Manuscripts must be double-spaced throughout the document on page sizes 8½ x 11 inches or A4. A margin of about 1 inch (2.5 cm) should be provided on all sides. All type should be 11-13 points in size, except as appropriate in tables and figures. Page numbers are required on Manuscript (main text) documents. Landscape format is acceptable as needed to display tables or figures to advantage.
- Word limits are not imposed on any manuscript types, but all papers should be concise, yet complete.
- All required or optional items for a submission are identified on the Attach Files page on the online submission form. Every table, figure, or video clip requires a separate electronic file; the "Description" column on the Attach Files page should provide the textual reference (e.g., 'Table 3'); this column is fully editable.
- No document can be submitted "offline."
- Use generic drug names throughout. Brand names may be inserted in parentheses following the generic names.
- The name and city/state/country of a drug or technology manufacturer must be included after the name of the product.
- **The author(s) or the name or geographical location of an author's institution(s) must not be identified in the text, header, or footer in the submission except on the Title Page and the Cover Letter.**
- **Acknowledgments must be placed at the end of the Title Page, not in the Manuscript document.**

## ONLINE DOCUMENTATION

**Online submission** requires that the submitted material be uploaded in several separate files. Online instructions will clarify what files are required. Details on preparation of file types follow.

1. A **Cover Letter** addressed to the Editor in Chief. The letter must include at the end a list of all authors as if for signature. Cover letters scanned from official letterhead with all signatures are strongly encouraged. The cover letter must state that the authors agree with and are responsible for the data presented. The letter should also describe or deny any potential conflicts of interest including commercial relationships such as consultation and equity interests.

2. **Title page** with (a) title of paper; (b) authors' full names with advanced degrees; (c) name(s) and geographical location of institution(s) in which work was done; (d) description of research support, if any; (e) information on the corresponding author: full name and advanced degrees, a reliable e-mail address, complete street address (not only P.O. box), telephone and fax numbers, and (f) any personal acknowledgements.

3. **For an Original Research article, a Structured Abstract; but for a Case Report, a Summary** (max. 200 words to indicate the clinical context and significance of the case, recapitulate the essential features, its outcome, and likely consequences for further study or clinical practice). A Structured Abstract will be published; a Summary is not published but is circulated to invited reviewers.

4. **Manuscript/main text** The Figure Legend list should be provided after the list of references and double-spaced. The Figures should be followed by Video Clips in this list. Each legend should include a title, notes to gloss abbreviations, and a permission statement for use of any copyrighted materials. Titles and notes for **tables** should not be in this list. Automatic reference systems may be used but are not required. The first reference to each source must be in Arabic numerical order. The reference list at the end of the article must also be in numerical order. The list headed "REFERENCES" should begin on a new page of the Manuscript document and be double-spaced. Use NLM-recognized title abbreviations for periodicals throughout as available listed online at <http://www.ncbi.nlm.nih.gov/journals> (based on those previously published by Index Medicus). References to abstracts, journal

supplements, and letters to editors must be identified as such. Inclusive page numbers of references are required. Online references should be integrated numerically with the other media in the References list; do not submit them parenthetically or as footnotes.

5. **Tables.** A separate file is required for each table, including its number and title at the top and any notes at the end. The notes should provide definition of abbreviations used in the table and permission notices for use of copyrighted materials. Tables should be formatted as Microsoft Word tables or Excel spread sheets, not in any graphic format. A table may be continued on multiple pages if necessary; do not repeat column headers on the additional pages.

6. **Figures.** A separate file is required for each figure, except for figures cited together and preferably to be seen adjacently (a-b etc.) **It is strongly preferred that figures be submitted in .tif (300 dpi), .eps, or .pdf format.** The highest possible quality is expected. **Authors are responsible to meet the graphic standards in Publisher's Author Artwork Instructions** (<http://www.elsevier.com/artworkinstructions>). A link to these Instructions is also provided on the Journal's home page. **Authors are strongly advised to consult these Instructions for detailed information before preparing figures.** The Publisher automatically provides for every submission or revision an Artwork Quality Assessment to inform authors of any likely problems with their figures. Figures not properly prepared will be returned to the contributor for revision or will be reworked with the cost charged to the contributor. Color figures are acceptable for papers dealing with color imaging; however, as color printing is costly, it will be used at the discretion of the Editor. Color used in bar, line, and pie graphs is discouraged; please substitute distinct shades of gray and /or patterned lines and shapes. If color images are to be reproduced in black and white, the contributor should submit the prints in black and white for best results.

7. **Video/audio clips.** The preferred movie/video format is .mpg, and the preferred audio format is .mp3. For additional information, follow the link to Author Artwork Guidelines on the home page of this web site. Video stills must be submitted as Figures.

## **SAMPLE REFERENCES**

### **Journal article, one to three authors**

1. Beutler E: The effect of methemoglobin formation on sickle cell disease. *J Clin Invest* 40:1856-1858, 1961
2. Karpatkin S, Smith K, Charnatz A: Heterogeneity of human platelets. III. Glycogen metabolism in platelets of different sizes. *Br J Haematol* 19:135-137, 1970

### **Journal article, four or more authors**

3. Golomb HM, Vardiman J, Sweet DL, et al: Hairy cell leukemia: Evidence for the existence of a spectrum of functional capabilities. *Br J Haematol* 38:161-162, 1968

### **Journal article in press**

4. O'Malley JE, Eisenberg L: The hyperkinetic syndrome. *Semin Psychiatry* (in press)

*(Note: A copy of the in-press article must be included as a Supplementary Manuscript file, described as "In-press, Reference [#].")*

### **Complete book**

5. Lillie RD: *Histopathologic Technic and Practical Histochemistry* (ed 4). New York, NY, Blakiston, 1965, pp 39-41

### **Chapter of book**

6. Moore G, Minowada J: Human hemopoietic cell lines: A progress report, in Farnes P (ed): *Hemic Cells in Vitro*, vol 4. Baltimore, MD, Williams & Wilkins, 1969, pp 100-105

### **Chapter of book that is part of published meeting**

7. Hatvlg JB, Kunkel HG, Gedde-Dahl T Jr: Genetic studies of the heavy chain subgroups of gamma globulin, in Killander J (ed): *Gamma Globulins, Proceedings of the Third Nobel Symposium*. New York, NY, Wiley, 1967, pp 19-26

### **Chapter of book that is part of unpublished meeting**

8. Polliak A: A morphologic study of the lymphoproliferative lesions induced by excess vitamin A. First Meeting, European Division, International Society of

Hematology, Milan, Italy, 1971, p 181

### **Abstract**

9. Curnutte JT, Karnovsky ML, Babior BM: Manganese-dependent NADPH oxidation by a particulate preparation from guinea pig granulocytes: An alternative interpretation. *Clin Res* 23:371A, 1975

### **Letter to Editor**

10. Seeler RA: Sick cell anemia monthly variations. *Blood* 47: 879, 1976

### **PROOFREADING**

Contributors are provided with electronic galley proofs and are expected promptly to proofread them for typesetting errors and to answer all queries. Important changes in data are allowed, but authors will be charged for excessive alterations in proof.

### **REPRINTS**

Reprints of articles can be furnished to contributors when ordered in advance of publication. An order form is sent in advance of proofs. Individuals wishing to obtain reprints of an article that appears in the *Journal* can do so by contacting the author at the address given in the *Journal*. Electronic copies may be purchased from the Publisher.

### **CARDIAC CALENDAR**

Announcements of meetings, conferences, and the like that are of interest to the readership of the *Journal* should be sent to the Section Editor for Cardiac Calendar, Dr. George Silvay (george.silvay@mountsinai.org), at least 3 months before the intended appearance of the notice. These announcements will be published only online.

*Updated Sept. 2012*