The relationship between metabolic acidosis, lactate, the lactate:pyruvate ratio, and outcome, in children with post-operative cardiogenic and septic shock

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Publication

Data presented in this thesis have been published in part in two peer-reviewed articles, Hatherill M, et al. Hyperchloaemic metabolic acidosis following open cardiac surgery. Archives of Disease in Childhood 2005;90:1288-1292 (sections of Chapter 2), and Hatherill M, et al. The lactate:pyruvate ratio following open cardiac surgery in children. Intensive Care Medicine 2007;33:822-829 (sections of Chapter 3). The author’s affiliation to Red Cross Children’s Hospital and the University of Cape Town, is acknowledged in these publications. Two additional manuscripts, containing data from chapters 4 and 5, are in preparation.
Abstract

Background

Measures of the severity of metabolic acidosis (base excess) and of the severity of the underlying acid-base derangements (levels of lactate, chloride, albumin, and strong ion gap) have been used to differentiate survivors from nonsurvivors in various types of adult critical illness, including states of severe haemodynamic compromise following cardiac surgery on cardiopulmonary bypass (CPB) and in septic shock. Prognostic studies of acid-base data for critically ill children in the settings of post-operative cardiogenic shock and septic shock are relatively scarce. It has been suggested that hyperchloremia might be a benign phenomenon that should not prompt escalation of therapy. Although it is recognised that hypoalbuminaemia is associated with adverse outcome, and obscures the extent of underlying metabolic acidosis, the significance of 'unmeasured' anions estimated from the strong ion gap remains controversial. It has been suggested that the admission lactate level is strongly predictive of paediatric intensive care unit (PICU) outcome in both shock states, but it is not known whether calculation of the lactate:pyruvate ratio would add prognostic value in children with either post-operative cardiogenic, or septic shock.

Aims

- To define underlying mechanisms of metabolic acidosis in children with post-operative cardiogenic shock and septic shock, using a combination of routine measured admission acid-base parameters and calculations based upon strong ion theory.
- To examine independent associations between underlying mechanisms and measures of PICU dependency and outcome.
- To develop a prognostic model for outcome based upon measured and calculated acid-base parameters using a multivariate statistical approach.
- To evaluate the prognostic benefit of calculating the ratio of lactate:pyruvate in children with these shock states.

Patients and setting

PICU of a university children's hospital in Cape Town, South Africa, which functions as the paediatric cardiology and cardiothoracic surgical referral centre
for the Western Cape Province (population 4 million). Between 250-300 paediatric cardiac operations are performed annually and approximately 170 are open cases on CPB. Children with septic shock are admitted directly from the children's hospital casualty, wards, and district hospitals. All children admitted with post-operative cardiogenic shock (February 2003 to March 2004) and septic shock (February 2003 to March 2005) were eligible for enrolment. The working definitions of post-operative cardiogenic and septic shock for study inclusion were intentionally broad, and based upon a clinical requirement for either additional intravascular volume replacement or inotropic support, following open cardiac surgery on CPB, or with severe sepsis, respectively.

Methods

Blood was sampled for routine arterial blood gas analysis and electrolytes, including sodium, potassium, calcium, magnesium, phosphate, chloride, lactate, and albumin, on admission to PICU. One mL blood was denatured in perchloric acid, and stored (-80 Celsius) for measurement of pyruvate by high performance liquid chromatography (HPLC). A Fendel-Stewart strong ion approach was used to derive calculated strong ion difference (SIDc), effective strong ion difference (SIDe), and strong ion gap (SIG). Components of the standard base excess contributed by albumin (BE alb), free water (BE fw), chloride (BE cl), and lactate (BE lact), were calculated using the equations of Giffin. Thresholds for clinically significant biochemical derangements were defined a priori as standard bicarbonate < 22 mmol/L, chloride > 110 mmol/L, SIG > 2 mmol/L, albumin < 30 g/L, lactate > 2 mmol/L, and lactate:pyruvate ratio > 20. Demographic data; measures of PICU dependency, including duration of ventilatory support, inotropic support, and PICU stay; and predicted and observed PICU outcome, were recorded.

Prevalence and severity of metabolic acidosis, and underlying hyperlactataemia, hyperchloremia, hypoalbuminaemia, and elevation of the SIG, was measured in children with each of the two shock states. Relationships with measures of PICU dependency and outcome were evaluated using crude statistical associations and odds ratios adjusted for confounding co-variables. Factors independently associated with elevation of the lactate:pyruvate ratio were analysed using
multivariate linear regression methods. In children with septic shock, prognostic value of acid-base variables was compared using area under the receiver operating characteristic (ROC) curves. A prognostic acid-base model for PICU outcome in septic shock was developed, using multivariate logistic regression methods.

**Results**

*Post-operative cardiogenic shock (n=97):* See chapters 2 and 3.

Median predicted mortality was 2%. A single nonsurvivor was observed. All children were mechanically ventilated and 95 (96%) received inotropic support, including 11 (11%) who received epinephrine infusion. This group of children had mild metabolic acidosis (median standard bicarbonate 20.1 mmol/L and base excess -5.1 mEq/L), characterised by hyperchloremia (median corrected chloride 113 mmol/L), and hypoalbuminemia (median albumin 30 g/L), but without a clinically significant increase in the strong ion gap (median SIG 0.7 mEq/L). The main contribution to the negative base excess (median -5.1 mEq/L) was chloride (median BE Cl -4.8 mEq/L), with a minor contribution by lactate and free water (median BE lact -0.3 mEq/L and BE fw -0.6 mEq/L), offset by the positive albumin component (median BE alb +3.4 mEq/L). Hyperchloremia was associated with reduced epinephrine requirement, with 3 (4%) hyperchloremic children receiving epinephrine, compared to 8 (28%) without hyperchloremia (p=0.005).

Mild hyperlactataemia occurred in 41 children (42%) and raised lactate:pyruvate ratio in 44 children (45%). Prevalence of raised lactate:pyruvate ratio among children with hyperlactataemia (56%) was similar to those with normal lactate (38%), (p=0.11). In the crude analysis, raised admission lactate was associated with longer CPB time (median 96 min vs 75 min), (p = 0.009), and increased requirement for epinephrine infusion (24% vs 2%) (p = 0.0006). Lactate:pyruvate ratio increased on average by 6.4 (95% CI 2.2 to 10.5) in children receiving epinephrine, and by 0.4 (95% CI 0.07 to 0.8) for every 10 minutes of aortic cross-clamp time. However, in a multiple linear regression model of the risk factors standard bicarbonate, lactate, and lactate:pyruvate ratio, only lactate was independently associated with prolongation of PICU support. On average,
The most common combination of obesity-pyruvate-oxidase were

in addition, these children demonstrated an elevated lactate-pyruvate ratio

independently associated with PICU outcome.

increase in odds of survival (86% CI 2 - 22%). Changes in PICU were not
survivors (86% CI 0.1 - 20%) and each 1 µmol increase in admission with an 1.1%
26%/% each 1 µmol increase in corrected cholate with 1.1% fall in odds of survival (65% CI 4 -
increase in lactate was associated with 1.5% fall in odds of survival (65% CI 4 -

Predicted survival with an area under the ROC curve = 0.84. Each 1 µmol

were of the form: log Odds of Survival = 15.2 - (0.71 x Weight) - (0.17 x

index of mortality (I). The final multiple regression logistic regression model

for admission: and 0.66 (86% CI 0.33 - 0.93) for predicted outcome (Pediatric

cholesterol: 0.52 (86% CI 0.36 - 0.69) for stroke on gap (0.5) (86% CI 0.36 - 0.69) for corrected
0.75 for lactate (86% CI 0.59 - 0.91) for age corrected

predicted survival curve was 0.65 (86% CI 0.39 - 0.91) for standard breastmilk:

cholesterol (median 7.5 mg/dL and lactate (median 2.3 mg/dL). Area under the

component was albumin (median 5.4 mg/dL), and negative components included

Medicated Predicted PICU Mortality was 0.30 and there were 27 non-survivors

(33%). The group of children demonstrated severe metabolic adresses (median

Medicated Predicted PICU Mortality was 0.30 and there were 27 non-survivors

Sepsis shock (n=53): See chapters 4 and 5

increase in admission lactate.

duration of PICU stay by 0.42 days (95% CI 0.04 - 0.79), for each 1 µmol

duration of mechanical ventilation by 0.27 days (95% CI 0.004 - 0.56); and

duration of intracranial pressure increased by 0.29 days (95% CI 0.06 - 0.52).
Lactate:pyruvate ratio increased on average by 4.4 (95% CI 4.0 – 4.8) for every 1 mmol/L increase in admission lactate; and fell by 1.1 (95% CI 1.0 – 1.2) for every 0.01 mmol/L increase in pyruvate. In the crude analysis, raised lactate:pyruvate ratio occurred in 59% of survivors (n = 33 / 56), compared to 62% of nonsurvivors (n = 22 / 27) (p = 0.07). In children with raised lactate (n = 63), the 52 children with raised lactate:pyruvate ratio had a similar proportion of survivors (n = 30; 58%), compared to the 11 children without raised lactate:pyruvate ratio (n = 7; 64%), (p = 0.99). In multivariate analysis, lactate:pyruvate ratio was not independently associated with outcome. Adjusted odds ratio for survival was 1.0 (95% CI 0.96 – 1.05) for each 1 unit increase in lactate:pyruvate ratio (p = 0.99).

Conclusions and recommendations

In children with post-operative cardiogenic shock following open cardiac surgery, who had low predicted and observed mortality, hyperchloreaemia was the predominant acid-base abnormality. Primary hyperlactataemia and strong ion gap-driven metabolic acidoses were rare. Hypoalbuminaemia was associated with prolonged inotropic support and intensive care stay. Hyperchloreaemia was associated with reduced requirement for epinephrine infusion, supporting the hypothesis that hyperchloreaemia following CPB may be a benign phenomenon. Although metabolic acidosis was mild and usually associated with hyperchloreaemia, elevation of the lactate:pyruvate ratio was common. Although, children with raised lactate:pyruvate ratio had longer aortic cross-clamp times and were more likely to receive epinephrine by infusion, only hyperlactataemia, not elevation of the lactate:pyruvate ratio, was independently associated with prolonged inotropic support, mechanical ventilation, and PICU stay.

Therefore, it is suggested that hyperchloreaemic metabolic acidosis should not prompt escalation of haemodynamic support in this setting. By contrast, raised admission lactate should suggest escalation of monitoring, evaluation of cardiac output, or inotropic support. Since calculation of the lactate:pyruvate ratio did not add useful prognostic information, measurement of pyruvate levels cannot be advocated in this clinical setting.
Children with septic shock, who had high predicted and observed mortality, showed severe acidaemia and metabolic acidosis, with moderate hyperlactataemia, hyperchloremia, and hypoalbuminemia. Most metabolic acidosis was of mixed etiology. In a multivariate logistic regression model, elevated lactate, elevated potassium, decreased albumin, and, contrary to the original hypothesis, increased corrected chloride, were independently associated with lower relative odds of survival. Elevated strong ion gap was not independently associated with PICU outcome or dependency, a finding that supports a benign view of this acid-base disturbance. Elevation of the lactate:pyruvate ratio was common, suggesting occult tissue hypoxia-ischaemia. However, after adjusting for co-variables, the lactate:pyruvate ratio was not independently associated with PICU survival, suggesting that the hyperlactataemia of hypoxia-ischaemia, and that of epinephrine-driven accelerated glycolysis, might have equally adverse prognostic significance.

In contrast to the setting of post-operative cardiogenic shock, metabolic acidosis due to raised lactate or raised chloride in septic shock should prompt the clinician to consider increased levels of monitoring or therapy. Metabolic acidosis due mainly to elevation of the strong ion gap should prompt efforts to identify the source of the 'unmeasured' anions, but should not necessarily indicate a need for escalation of therapy. Given the lack of prognostic association between the lactate:pyruvate ratio and outcome, measurement of pyruvate cannot be recommended as a tool to predict PICU outcome in children with septic shock.
Prologue

The paediatric intensivist is often faced with critically ill children who may have the same diagnosis, and similar severity of illness, on their arrival in the Paediatric Intensive Care Unit (PICU), yet some of these children survive to be discharged home, while others progress to multi-organ failure and death. The challenge of identifying which children are at greatest risk, so that they may be treated early and aggressively, is particularly urgent in the presence of the haemodynamic instability associated with both cardiac surgery and severe sepsis [1]. Although traditional paediatric scoring systems have incorporated blunt measures of the severity of metabolic acidosis into prognostic tools, many questions regarding the relationship between the underlying mechanism of the acidosis and outcome still need to be answered[2]. In particular, the early work of Well and Affifi on the prognostic value of lactate and the lactate:pyruvate ratio has yet to be fully explored in the setting of critically ill children with shock states of different aetiology[3].

Research Questions

The investigations upon which this thesis is based were designed to answer three principal research questions:

1) What are the commonest reasons for metabolic acidosis in children with shock (a) after open cardiac surgery; and (b) severe sepsis?

2) Which of these underlying mechanisms are associated with outcome in the two shock states?

3) Is lactate the principal determinant of bad outcome, and if so, does calculation of the ratio of lactate:pyruvate have additional prognostic value?
Specific Aims

The primary specific aims were:

1) To define prospectively the underlying mechanisms of metabolic acidosis on admission to PICU in children with (a) post-operative cardiogenic shock; and (b) septic shock, using a combination of routinely measured acid-base parameters and calculations based upon Strong Ion Theory. Hypothesis: The predominant mechanisms underlying metabolic acidosis are: (a) hyperchloremia in post-operative cardiogenic shock; and (b) hyperlactatemia in septic shock.

2) To examine the independent associations between these underlying mechanisms and measures of PICU dependency and outcome. Hypothesis: Hyperchloremia is independently associated with good outcome, and hyperlactatemia with bad outcome, in both (a) post-operative cardiogenic shock; and (b) septic shock.

3) To evaluate the prognostic benefit of calculating the ratio of lactate:pyruvate in children with these shock states. Hypothesis: Elevation of the lactate:pyruvate ratio adds prognostic value in children with (a) post-operative cardiogenic shock; and (b) septic shock.

The secondary specific aim was:

4) To develop a prognostic model for outcome based upon routinely measured and calculated acid-base parameters at the time of admission to PICU, using a multivariate statistical approach. Hypothesis: A multivariate regression model based upon selected acid-base parameters, such as the admission lactate level, may have prognostic value similar to, or greater than, conventional paediatric scoring systems.

Methodological approach

The study upon which this thesis is based consists of investigations conducted in children with shock during the period February 2003 to March 2005. Participants were enrolled at the time of their admission to the PICU at Red Cross Children's
Hospital during the duty periods of the principal investigator. The PICU has physical capacity for 18-22 beds, admits approximately 1200 children per year, and has full-time paediatric intensivist cover. The children's hospital functions as one of two paediatric referral centres for the Western Cape Province, which has a population of approximately 4 million people, and is the affiliated paediatric academic hospital of the University of Cape Town. The study was approved by the Research Ethics Committee of the University of Cape Town (Reference: 157/2002) and informed consent was obtained from a parent or guardian for participation. The study is divided into four sub-sections, designed to answer the specific aims above:

A. An evaluation of the common underlying mechanisms of metabolic acidosis and their prognostic significance in children with post-operative cardiogenic shock (Primary Specific Aims 1 and 2), which is described in Chapter 2.

B. An evaluation of the relationship between lactate, the lactate:pyruvate ratio, and outcome in children with post-operative cardiogenic shock (Primary Specific Aim 3), which is described in Chapter 3.

C. An evaluation of the common underlying mechanisms of metabolic acidosis and their prognostic significance in children with septic shock (Primary Specific Aims 1 and 2); and development of a multivariate prognostic model (Secondary Specific Aim 4), which are described in Chapter 4.

D. An evaluation of the relationship between lactate, the lactate:pyruvate ratio, and outcome in children with septic shock (Specific Aim 3), which is described in Chapter 5.

The first two investigations were carried out concurrently in children undergoing cardiac surgery during the 1-year period from February 2003 to March 2004, and data were analysed during 2004 and 2006, respectively. The latter two investigations were carried out concurrently in children with septic shock during the 2-year period from February 2003 to March 2005, and data were analysed during 2006 and 2007, respectively. Methodology is discussed in specific detail in Chapters 2 to 5.
Presentation of findings

The format in which the findings are presented in this thesis follows the same chronological order as the study investigations, in order to maintain focus on the logical sequence of the research questions, while maintaining a coherent narrative. Whenever possible, results are presented in tabular or figurative form, rather than paragraphs of text, for the sake of clarity and brevity.

An overview of the relevant acid-base literature is summarised in Chapter 1. Study investigations, and the background literature relevant specifically to those investigations, are presented in Chapters 2 to 5. A summary of the main findings and lessons for clinical practice are presented in Chapter 6.

Contributions

The principal investigator and author conceived and planned the study; performed the literature search; consented and enrolled the participants; collected and stored the study samples; recorded the study data; undertook statistical training (University of Cape Town, MPH Biostatistics modules I, II, and III) and performed all statistical analyses; collated and presented the results; and wrote the thesis.

The author is grateful for the assistance of the medical and nursing staff of the PICU with screening of potential participants. Routine laboratory analyses were conducted by the NHLS laboratory at Red Cross Children's Hospital, and additional study-specific laboratory analyses (pyruvate levels) were performed on a fee-for-service basis by Ampath Laboratories, Pretoria, through Pathcare Laboratories, Cape Town.
Chapter 1
An overview of acid-base derangements and outcome prediction in critical illness.

Standard bicarbonate and base deficit
Historically, non-respiratory or metabolic acidosis has been analysed using either the standard bicarbonate-based approach of the Boston school, or the base excess approach of Siggard-Andersen and the Copenhagen school[4]. Although echoes of the Great Trans-Atlantic Acid-Base Debate may linger and proponents of each approach are unreconciled, many critical care researchers have routinely used the standard bicarbonate level to define metabolic acidosis, and the base excess to evaluate the severity of that metabolic acidosis[4-7]. For example, several authors have described associations between the severity of metabolic acidosis (as measured by the base deficit), shock, and mortality, in animal models, and in patients with trauma and other heterogeneous critical illnesses[5-7].

The ready availability and ease of base excess measurement, which is offered by on-site arterial blood gas analysis, has led to proposals that base excess should be used to guide clinical decision-making in the setting of major trauma and critical illness in adults[8, 9]. In paediatric practice, measurement of the base excess was incorporated into paediatric mortality risk scoring systems and guidelines for advanced paediatric life support[2, 10]. However, other authors have demonstrated, for example in adult surgical ICU patients, that the admission base excess is a poor predictor of ICU survival, in contrast to the underlying causes of metabolic acidosis, such as hyperchloremia or hyperlactataemia, which may actually be associated with ICU outcome[11, 12].

Lactate
Lactate metabolism is an intricate component of cellular energy production by generation of ATP[13, 14]. Under normal physiological conditions, the majority of ATP is generated by metabolism of glucose via the process of oxidative phosphorylation, beginning with cytoplasmic conversion of glucose to pyruvate, conversion of pyruvate to acetyl CoA by pyruvate dehydrogenase, and mitochondrial oxidation via the Krebs cycle[13, 14]. However, when mitochondrial energy production by oxidative phosphorylation is limited by cellular hypoxia, ATP is supplemented by anaerobic glycolysis, resulting in the
formation of a relatively small amount of ATP, and lactate[13, 14]. When aerobic oxidation is limited by cellular hypoxia, lactate production is accelerated by build up of reduced nicotinamide adenine dinucleotide (NAD), which shifts the reversible lactate dehydrogenase reaction in favour of conversion of pyruvate to lactate[3, 14]. This phenomenon corresponds to the traditional clinical classification of type A lactic acidosis associated with hypoxia[15].

We would expect that if critical illness and shock are associated with global or regional hypoperfusion that results in cells being exposed to a state of hypoxia, then associations between the admission lactate and outcome would be found. Indeed, relationships between hyperlactataemia and mortality have been described in critical illness among neonates, children, and adults[16-19]. For example, Deshpande and colleagues showed in critically ill neonates that the base excess could not be used as a proxy measure for the lactate level, and that lactate might be a useful predictor of mortality in these infants[17]. The author has also demonstrated in a previous retrospective study, among a heterogeneous group of critically ill children, that the presence of early hyperlactataemia might be used to predict PICU mortality[19]. These findings have also been confirmed in adults. Stacpoole reported only 59% survival after 24 hours among critically ill adults with metabolic acidosis and lactate levels greater than 5 mmol/L on admission to the ICU[18]. Lastly, Husain and co-workers showed that in contrast to the base excess, the admission lactate and the lactate clearance time could be used to differentiate survivors and nonsurvivors in adult surgical ICU patients[12].

However, the critical question is whether the traditional type A hypoxic mechanism of lactate production fully accounts for the prognostic associations seen in critically ill patients[15]. Several recent studies have challenged the hypoxia-ischaemia paradigm in both post-operative cardiogenic shock and septic shock, and differentiated the causes of hyperlactataemia between accelerated lactate production and decreased lactate clearance[20, 21]. In doing so, these studies have provided a common link between mortality, hyperlactataemia, and glucose metabolism, in two shock states with very different pathogenesis. Therefore, although much effort has been expended on attempts to control lactate and glucose levels in the critically ill, it is possible that these efforts should instead be focused on potential underlying mechanisms, including epinephrine-
driven glycolysis[18, 20-25]. These concepts will be examined in more detail in chapters 3 and 5.

‘Unmeasured anions’

In the last decade, the Great Trans-Atlantic Debate has been replaced by the Great Stewart Debate, in which proponents of Stewart’s Strong Ion Theory appear to discard basic tenets of acid-base analysis, by relegating hydrogen ions and bicarbonate to the level of dependent variables, the concentrations of which are determined solely by the relative concentration of fully dissociated anions and cations (Strong Ion Difference or SID), the concentration of weak acids (mainly albumin), and dissolved carbon dioxide[4, 26]. The methodology of the strong ion approach to acid-base analysis and partition of the base excess is dealt with extensively in the literature and therefore, only those aspects that are directly relevant to this analysis will be discussed in more detail[27-36].

It should be acknowledged that the Stewart model has been criticised by some authorities, including Siggaard-Andersen, as a return to ‘archaic’ definitions of acids and bases as equivalent to anions and cations[39]. Although the underlying basis of Stewart Theory is not entirely novel, since SID is analogous to the historical concept of Buffer Base, the undeniable value of the strong ion approach is that it provides a conceptual framework within which the underlying causes of a metabolic acid-base disturbance can be compartmentalised, compared, and analysed for prognostic associations[29, 39]. Critical care researchers, in particular, have recognised in Stewart Theory an ideal tool with which to understand the complex acid-base derangements in critically ill patients with shock and multi-organ dysfunction[29, 33, 40-43]. Although it could be argued that the primary benefit of Strong Ion Theory is that it focused attention on the contributions of chloride and albumin to changes in metabolic acid-base status in common clinical situations, much attention has been paid to the ‘unmeasured’ anions that contribute to the strong ion gap (SIG)[28-31, 33, 40, 43-45].

Some authors have utilised the methodology of Stewart to describe disturbances of these ‘unmeasured’ anions, estimated from the strong ion gap, among critically ill children and adults[28, 29, 33, 40, 44]. It is notable from these studies that severe derangements of ‘unmeasured’ anions were often not detected by conventional measures of metabolic acidosis, such as the base excess and traditional anion gap, due
to the alkalining effect of co-existing hypoalbuminaemia[29, 30, 33, 44]. The ability to estimate the amount of 'unmeasured' anions from the strong ion gap gave impetus to the hypothesis that these anions, more so than lactate, might predict irreversible tissue injury, multi-organ failure, and mortality[40]. Since 'unmeasured' anions were thought to be metabolised in part by the visceral circulation, microvascular ischaemia and occult hepatic cellular injury were some of the mechanisms proposed to support this hypothesis[46, 47].

In clinical studies, Balasubramanyan and colleagues showed in a heterogeneous group of critically ill children that 'unmeasured' anions were a better predictor of mortality than the base excess[40]. However, in common with other studies, interpretation of these findings is complicated by the fact that calculation of the strong ion gap to derive the 'unmeasured' anion effect also included lactate, a parameter that is now measured routinely in critical care practice[37, 40, 48]. This illustrates the problems inherent in comparison of strong ion gap findings with those of other studies that treat lactate separately, as a 'measured' anion, outside of the strong ion gap[34, 42, 49]. Unless explicitly stated, the term 'unmeasured' anions used in this thesis refers to the truly 'unmeasured' anions, other than lactate.

The equations needed to derive strong ion gap, and thus estimate 'unmeasured' anions, proved cumbersome in clinical practice, and for this reason many authors have used abbreviated versions of the classical Stewart equations, and focused on partition of the net measured base excess to derive the base excess contribution due to 'unmeasured' anions[35, 37]. Others have referred to the concept of the combination of 'unmeasured' anions and lactate as tissue acids or tissue anions[28, 33]. However, it is important to note that calculation of the strong ion gap is not a direct reflection of the amount of 'unmeasured' anions, since it represents the net difference between the amount of 'unmeasured' anions and 'unmeasured' cations, which, admittedly, may be quantitatively less important in physiological states[26]. Estimation of the true contribution of 'unmeasured anions' to the base excess in children is further complicated by the routine use of adult norms by arterial blood gas analysers [41, 50, 51]. It is apparent that use of the accepted adult reference value for bicarbonate (24.8 mmol/L), which is greater than the average bicarbonate found in infants (= 22 mmol/L), would result in a small but systematic overestimation of the true negative base excess and the strong ion gap[33].
For the reasons above, it is not surprising that attempts to predict outcome using strong ion gap methodology have met with conflicting results in several large studies among critically ill patients[52-54]. In a heterogeneous group of critically ill adults, Cusack et al showed that the strong ion gap had no predictive value for mortality, in contrast to the base excess and lactate, which were relatively good predictors[52]. Rocktaeschel showed in a similar patient group that the strong ion gap had only modest value in predicting hospital mortality (area under ROC curve = 0.63), and that even this effect was not apparent after adjusting for potential confounders in a multivariate logistic model[54]. By contrast, Kellum reported that strong ion gap was the best discriminator of outcome after major vascular trauma, and Dondorp showed that strong ion gap was a powerful prognostic indicator in a large study of adults with severe falciparum malaria[53, 55]. Therefore, the true value of measurement of the strong ion gap and estimation of 'unmeasured' anions for prediction of outcome, particularly in children with shock states, remains uncertain.

**Albumin**

Apart from estimation of 'unmeasured' anions derived from calculation of the strong ion gap, the Stewart approach allows identification and quantification of the other components that contribute to a measured metabolic acidosis, such as the chloride and albumin components[28, 30-32]. The author and others have previously reported that unless the alkalinising effect of hypoalbuminaemia is taken into account, using either the classical Stewart approach, or adjustment of the anion gap as proposed by Figge, severe metabolic acid-base derangements can be under-estimated[30, 31, 33, 44]. Given that hypoalbuminaemia is common in critical illness, and is a significant independent predictor of mortality, the confounding effect of this parameter should also be assessed in any prognostic study among critically ill patients[33, 44, 56].

**Sodium and chloride**

Assessment of the relative imbalance between the strong ions sodium and chloride is a crucial element of the Stewart approach to acid-base analysis, whether using the classical approach, or abbreviated approaches suggested by other authors[28, 32, 37]. However, a lack of consistency between these methods has also made direct comparison of the effect of hyperchloaraemic metabolic acidosis on morbidity and
mortality somewhat difficult[28, 32, 37, 49]. Some authors have calculated the
contribution of a relative excess of chloride to the base excess, but used different
formulae[35, 37, 40]. Other authors have used variation in the ratio of chloride to sodium
as an alternative measure[28]. In an attempt to link the relative excess of chloride to
readily recognisable reference values, and to make the analysis user-friendly to
clinicians, some authors have adjusted the measured chloride for the measured sodium,
and derived a corrected chloride level, the excess of which denotes hyperchloraemia for
the purpose of acid-base analysis[32, 49]. The small base excess contribution of
dilutional acidosis due to free water may also be calculated separately, but this step has
not been considered necessary in some abbreviated approaches, if the corrected
chloride value is used[37, 49]. However, another major stumbling block to comparison of
chloride effects across studies is that, whereas some authors have used the traditional
reference value for chloride of 102 mmol/L, others, in institutions where ion-specific
electrodes are used to measure chloride levels, have used the technique-specific
reference value of 108 mmol/L[32, 35, 37, 40]. In this thesis, hyperchloraemic acidosis is
identified on the basis of the corrected chloride level, and the contribution of the chloride
effect towards a metabolic acidosis is calculated using a full partitioned base excess
approach[32, 57, 58].

Notwithstanding the variety of approaches to evaluation of the chloride effect, several
authors have demonstrated associations between hyperchloraemia and ICU
outcome[11, 49, 53, 54]. Brill and colleagues showed that among adult surgical intensive
care patients, those with hyperchloraemic acidosis had a lower mortality (10%) than
those with metabolic acidosis due to other factors (48%)[11]. Rocktaeschel and Dondorp
have reported that uncorrected chloride levels are higher in survivors of critical illness
and patients with severe malaria, respectively, although these associations are no longer
significant when adjusted for confounders in a multivariate model[53, 54]. The author
has also previously reported a trend towards survival associated with hyperchloraemic
acidosis among a heterogeneous group of children with shock[49]. Although the
mechanism for such a protective effect is not clear, it has been suggested that
hyperchloraemic acidosis may represent renal sodium loss relative to chloride in
reversible, ie. benign, renal failure, or that hyperchloraemia per se is a physiological
renal compensatory mechanism to adjust for metabolic alkalosis due to
hypoalbuminaemia[28, 49]. The association between nosocomial hyperchloraemic
acidosis and administration of intravenous fluids containing 0.9% saline, which contains a relative excess of chloride in a 1:1 ratio with sodium, is well documented[43, 59]. However, it must be noted that a benign view of hyperchloremic acidosis conflicts with evidence from animal models, in which a moderate-severe titrated hyperchloremic acidosis was associated with hypotension and increased circulating levels of inflammatory cytokines, such as interleukin-6, interleukin-10, and tumour necrosis factor[60, 61].

The chapters that follow will examine, in turn, the prevalence and clinical significance of metabolic acidosis, and the most common underlying acid-base derangements, including hyperchloremia and hyperlactataemia; and the additional value of calculation of the lactate:pyruvate ratio, in two distinct groups of haemodynamically unstable children: those with post-operative cardiogenic shock, and those with septic shock. In the latter group, a multivariate predictive regression model utilising only admission acid-base parameters will be developed as a guide to ICU prognosis in children with septic shock.
Chapter 2

Metabolic acidosis and outcome in children with post-operative cardiogenic shock

Introduction

Metabolic acidosis after cardiac surgery

The post-operative period following cardiac surgery on cardiopulmonary bypass (CPB) is a unique situation, in which the twin insults of cardiopulmonary bypass and operative trauma to the myocardium may result in haemodynamic instability, inotrope-dependence, multi-organ failure, and death in the early post-operative period[62-66]. Therefore, it is not surprising that the presence of metabolic acidosis in a child following cardiac surgery might prompt the clinician to escalate haemodynamic support, based on the traditional assumption that metabolic acidosis signifies low cardiac output, poor tissue perfusion, and increased risk of adverse events[5, 7, 63-65]. However, there are pitfalls in this approach, since outcome in critically ill children may depend primarily on the underlying mechanism (raised lactate, chloride, or 'unmeasured' anions), rather than the magnitude of the metabolic acidosis measured by the standard bicarbonate or the base excess[49].

Hyperlactataemia following cardiac surgery has traditionally been associated with post-operative adverse events and mortality[62-64, 66]. However, it is increasingly accepted that mild lactic acidosis following cardiac surgery on CPB does not necessarily signify regional tissue hypoxia, or intraoperative oxygen debt, since it may be influenced by confounding factors such as glycolytic flux or pyruvate dehydrogenase inhibition[67-69]. For example, Ganuechak and colleagues have demonstrated that systemic oxygenation was not at all impaired during CPB in adults undergoing coronary artery bypass graft surgery[67]. The mechanism of post-operative metabolic acidosis may also be influenced by the choice of fluid used to prime the CPB circuit, contributing to hyperlactataemia, hyperchloremia, or elevation of 'unmeasured' anions[70-73]. Laskaer and colleagues showed that patients undergoing CPB developed iatrogenic metabolic acidosis immediately on delivery of the pump prime fluids[71]. However, the mechanism of the metabolic acidosis was determined by the content of the pump prime, being due to 'unmeasured' anions (acetate and gluconate) when PlasmaLyte 148 was used, and due
to hyperchloremia when Haemaccel-Ringers was used[71]. Himpe and colleagues also demonstrated that 'unmeasured' anions increased significantly on CPB, as did the lactate level, but the resultant metabolic acidosis resolved by the end of CPB only in those receiving lactate-containing pump prime[70].

In contrast to hyperlactataemia, the clinical significance of hyperchloremic and 'unmeasured' anion metabolic acidosis, following cardiac surgery with CPB, are less clear, since some of the existing evidence is difficult to interpret[41, 51, 62-64, 66]. For example, Durward and colleagues showed in a group of 85 children undergoing CPB surgery that a higher strong ion gap, lower base deficit, and higher lactate level, were good predictors of post-operative ICU mortality based on the area under the receiver operating characteristic (ROC) curve[41]. However, since the mortality rate was only 5.8%, the confidence intervals were predictably wide[41]. Nevertheless, although one third of patients showed hyperchloremia, it is notable that a low chloride level relative to sodium was also associated with reasonable predictive value for post-operative ICU mortality, with area under the ROC curve of 0.75, comparable to that of the PIM 1 score at 0.85[41]. Murray and co-workers also studied a heterogeneous group of 44 children undergoing both open cardiac surgery (on CPB) and closed cardiac surgery (off CPB), and reported that 'unmeasured' anions were responsible for metabolic acidosis in 73% of samples, hyperlactataemia in 10%, and hyperchloremia in 13% (and in 48% of samples immediately on admission to ICU)[51].

The inference from previous work is that if a clinician were to have escalated haemodynamic support for a child with a post-operative metabolic acidosis, in a scenario similar to that described by Durward et al, the clinician might have acted correctly if the acidosis were driven by 'unmeasured' anions, or lactate, but incorrectly if it were driven by hyperchloremia[41]. The dangers of escalating therapy in the face of a chloride-driven post-operative metabolic acidosis are illustrated by the potential to aggravate that state, by administration of intravenous resuscitation fluids with excess chloride content, such as 0.9% saline[43].
Aims
The aims of the investigations described in this chapter were to delineate the underlying mechanism and clinical significance of acid-base derangements in children with post-operative cardiogenic shock following open cardiac surgery, in terms of a modified Fenn-Stewart strong ion approach[26, 29-32, 34]. Clinical significance was to be assessed by examining the relationships between specific acid-base abnormalities, particularly those due to mechanisms other than hyperlactataemia, measures of ICU dependency, and post-operative mortality. The initial hypothesis was that metabolic acidosis following open cardiac surgery in children is more often due to hyperchloremia, rather than hyperlactataemia; and secondly, that hyperchloremic metabolic acidosis is a benign phenomenon that should not prompt escalation of cardiac support in the immediate post-operative period.

Materials and Methods
The study was set in the PICU of a university children's hospital in Cape Town, South Africa, which functions as the paediatric cardiology and cardiothoracic surgical referral centre for the approximately 4 million people living in the Western Cape Province. Between 250-300 paediatric cardiac operations are performed per annum, of which approximately 170 are open cases using CPB. Neither surgical palliation of hypoplastic left heart syndrome (Norwood procedure), nor extracorporeal membrane oxygenation (ECMO), are currently offered at this centre.

Ethical approval for the study was obtained from the university ethics committee. All children admitted to the PICU following CPB for surgical correction of congenital or acquired heart defects from February 2003 to March 2004 were screened for enrolment, during the duty periods of the principal investigator. Cardiopulmonary bypass and post-operative cardiogenic shock were the only screening criteria for eligibility, and children were not pre-selected on the basis of specific anatomical cardiac defect or type of surgery. The clinical definition of post-operative cardiogenic shock was intentionally broad, and included all children who had undergone cardiac surgery on CPB, and who, in addition, received either fluid resuscitation, or inotropic support, on admission to the PICU. Cardiac output was not specifically measured or estimated, by invasive or non-invasive techniques, and therefore this clinical definition includes children who might
have been started on inotropic support empirically in the operating theatre, on the basis that post-operative low cardiac output syndrome would have occurred in the absence of such support[65].

The fluid used to prime the CPB circuit (the 'pump prime') was usually a mixture of blood and Stabilized Human Serum (SHS), a colloid prepared by the regional blood transfusion service (Western Province Blood Transfusion Service, Parow, South Africa). In children with severe pre-operative polycythaemia, the pump prime consisted of SHS alone. SHS contains 36 g/L albumin, 13 g/L immunoglobulin, 130 mmol/L sodium, and 130 mmol/L chloride. Blood and SHS were also the fluids of choice for intra-operative volume resuscitation, rather than 0.9% saline or Ringer's lactate.

Immediately on admission to PICU, blood was routinely sampled for arterial blood gas (ABG) analysis and electrolytes. Blood pH, pCO₂, bicarbonate, and standard base excess were measured and derived using a Radiometer ABL 520 blood gas analyser (Copenhagen, Denmark). The equations used by the Radiometer ABL 520 blood gas analyser to derive standard base excess and standard bicarbonate are shown in full in Appendix 1. These equations are based on adult norms for bicarbonate levels, reflecting routine clinical practice in the PICU and allowing direct comparison with other studies in children[17, 41, 50, 51]. Serum electrolytes (sodium, potassium, calcium, magnesium, phosphate) were measured by the ion-specific electrode method using a Beckman CX9 Pro analyser (Berlin, Germany). Serum lactate was measured by the enzymatic method using a Beckman CX5 analyser (Berlin, Germany). Serum albumin was measured by the reagent method using a Beckman CX9 Pro analyser (Berlin, Germany).

A Fenn-Stewart approach, with the modifications of Figge, was used to derive calculated strong ion difference (SIDc), effective strong ion difference (SIDe), and strong ion gap (SIG)[26, 29-31, 34]. Chloride was corrected for free water (cCl) to a serum sodium of 140 mmol/L, by multiplying the measured chloride:sodium ratio by a factor of 140[32, 49]. Metabolic acidosis was defined as standard bicarbonate (SB) < 22 mmol/L and other clinically significant biochemical derangements were defined a priori as albumin < 30 g/L, chloride > 110 mmol/L, lactate > 2 mmol/L, and strong ion gap (SIG) > 2 mmol/L[49]. See Table 2.1.
Table 2.1: Equations and Definitions: Acid-base abnormalities.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Equation/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Standard bicarbonate &lt; 22 mmol/L</td>
</tr>
<tr>
<td>Corrected chloride (cCl)</td>
<td>140 x Cl / Na</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>cCl &gt; 110 mmol/L</td>
</tr>
<tr>
<td>Raised lactate</td>
<td>&gt; 2 mmol/L</td>
</tr>
<tr>
<td>Raised strong ion gap (SIG)</td>
<td>&gt; 2 mmol/L</td>
</tr>
<tr>
<td>Low albumin</td>
<td>&lt; 30 g/L</td>
</tr>
<tr>
<td>SIDc</td>
<td>Na + K + Ca + Mg – (Cl + lactate)</td>
</tr>
<tr>
<td>SIDe</td>
<td>Bicarbonate + PO4 charge + albumin charge</td>
</tr>
<tr>
<td>SIG</td>
<td>SIDc – SIDe</td>
</tr>
</tbody>
</table>

*Partition of the base excess*

The individual components of the standard base excess (BE) contributed by albumin (BE alb), free water (BE fw), chloride (BE cl), and lactate (BE lact), were calculated using the equations of Gliffix, incorporating normal values for the ion-sensitive electrode method[32, 57, 58]. For the purposes of these calculations, reference values were taken as albumin 42 g/L, sodium 140 mmol/L, chloride 108 mmol/L, and lactate 1.5 mmol/L[57, 58]. See Table 2.2

Table 2.2: Equations and Definitions: Calculated components of total base excess (BE)

<table>
<thead>
<tr>
<th>Component</th>
<th>BE formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>[BE (alb)] = (0.123 x pH – 0.631) x (42 – albumin)</td>
</tr>
<tr>
<td>Free water</td>
<td>[BE (fw)] = 0.3 x (Na – 140)</td>
</tr>
<tr>
<td>Chloride</td>
<td>[BE (cl)] = 108 – Cl</td>
</tr>
<tr>
<td>Lactate</td>
<td>[BE (lact)] = 1.5 - lactate</td>
</tr>
</tbody>
</table>
Median CPB time was 80 min (17-232) and median aortic cross-clamp time was 46 min (0-149). Aortic cross-clamp time had weak, but statistically significant, associations with the variation in admission lactate (slope +0.008; R² 0.03; p<0.0001); cCl (slope +0.027; R² 0.04; p<0.0001); SiG (slope -0.020; R² 0.02; p=0.05); and albumin (slope -0.016; R² 0.01; p<0.0001).

Acid-base data immediately on admission to PICU after cardiac surgery are shown in Table 2.4.

Table 2.4: Admission acid-base data (n=97)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>median</th>
<th>(range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.38</td>
<td>(7.17 - 7.61)</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>-5.1</td>
<td>(-12.9 to +2.5)</td>
</tr>
<tr>
<td>SB (mmol/L)</td>
<td>20.1</td>
<td>(10.6 - 28.8)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>30</td>
<td>(16 - 44)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.8</td>
<td>(0.7 - 9.1)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138</td>
<td>(129 - 146)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>111</td>
<td>(97 - 121)</td>
</tr>
<tr>
<td>cCl (mmol/L)</td>
<td>113</td>
<td>(101 - 126)</td>
</tr>
<tr>
<td>SIDc (mEq/L)</td>
<td>31.7</td>
<td>(19.7 - 46.5)</td>
</tr>
<tr>
<td>SiDe (mEq/L)</td>
<td>31.1</td>
<td>(22.9 - 40.9)</td>
</tr>
<tr>
<td>SIG (mEq/L)</td>
<td>0.7</td>
<td>(-13.7 to +14.8)</td>
</tr>
</tbody>
</table>

Overall, this group of children demonstrated mild metabolic acidosis (median standard bicarbonate 20.1 mmol/L and base excess -5.1 mEq/L) characterised by hyperchloremia (median cCl 113 mmol/L). Half of the patients demonstrated clinically significant hypoalbuminaemia (median albumin 30 g/L). There was no clinically significant excess of ‘truly unmeasured’ anions or cations (median SiG 0.7 mEq/L).
**Partitioned base excess (BE)**

Calculated components of the total base excess are shown in Table 2.5.

**Table 2.5: Calculated components of total base excess.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>median</th>
<th>(range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE ( alb)</td>
<td>+3.4</td>
<td>(-0.6 to +6.8)</td>
</tr>
<tr>
<td>BE (fw)</td>
<td>-0.6</td>
<td>(-3.3 to +1.8)</td>
</tr>
<tr>
<td>BE (cl)</td>
<td>-4.8</td>
<td>(-18 to +7.2)</td>
</tr>
<tr>
<td>BE (lact)</td>
<td>-0.3</td>
<td>(-7.6 to +0.8)</td>
</tr>
</tbody>
</table>

The primary individual determinants of the total base excess were chloride and albumin. The predominant contribution to the negative total base excess (median base excess - 5.1 mEq/L) was the chloride component (median BE cl -4.8 mEq/L), with a minor contribution by lactate and free water (median BE lact -0.3 mEq/L and BE fw -0.6 mEq/L). The negative base excess contributions were partly offset by the positive albumin component (median BE alb +3.4 mEq/L). The median base excess component due to the net effect of other measured (calcium, magnesium, phosphates) and truly 'unmeasured' cations and anions was -1.6 mEq/L.

**Albumin**

Forty-six children had clinically significant hypoalbuminaemia (47%). Hypoalbuminaemia was associated with a longer duration of inotropic support, median 3 days (1-10) compared to 2 days (0-10) (p=0.047), and longer duration of PICU stay, median 4 days (2-11) compared to 3 days (2-20) (p=0.009). There was no significant association between hypoalbuminaemia and increased adrenaline requirement (p=0.14), CPB time (p=0.55), aortic cross-clamp time (p=0.29), predicted mortality (p=0.17), or duration of mechanical ventilation (p=0.06) (data not shown).
**Metabolic acidosis**

Seventy-two children (74%) had a metabolic acidosis on admission to PICU. The presence of metabolic acidosis was not associated with increased adrenaline requirement (p=0.69), CPB time (p=0.52), aortic cross-clamp time (p=0.61), predicted mortality (p=0.35), duration of mechanical ventilation (p=0.99), duration of inotrope support (p=0.53), or duration of PICU stay (p=0.65) (data not shown).

Prevalence of individual metabolic acid-base abnormalities are shown in Table 2.6.

**Table 2.6: Prevalence of individual metabolic acid-base abnormalities.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoalbuminaemia</td>
<td>46</td>
<td>(47%)</td>
</tr>
<tr>
<td>Hyperchloraemia</td>
<td>88</td>
<td>(70%)</td>
</tr>
<tr>
<td>Hyperlactataemia</td>
<td>41</td>
<td>(42%)</td>
</tr>
<tr>
<td>Elevated SIG</td>
<td>39</td>
<td>(40%)</td>
</tr>
<tr>
<td><strong>Metabolic acidosis</strong></td>
<td>72</td>
<td>(74%)</td>
</tr>
<tr>
<td><strong>Single primary aetiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperchloraemia</td>
<td>24</td>
<td>(33%)</td>
</tr>
<tr>
<td>Hyperlactataemia</td>
<td>1</td>
<td>(1%)</td>
</tr>
<tr>
<td>Elevated SIG</td>
<td>9</td>
<td>(13%)</td>
</tr>
<tr>
<td><strong>Mixed aetiology</strong></td>
<td>38</td>
<td>(53%)</td>
</tr>
<tr>
<td>Hyperchloraemia</td>
<td>29</td>
<td>(40%)</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>(13%)</td>
</tr>
</tbody>
</table>

There was a single primary cause for the metabolic acidosis (n=72) in 34 children (47%). The primary cause of metabolic acidosis was hyperchloraemia in 24 children (33%). Other primary causes of metabolic acidosis were rare, with raised lactate in 1 child (1%), and raised SIG in 9 children (13%). The cause of the metabolic acidosis was mixed in 38...
children (53%), in whom hypercholaemia was one of the causative factors in 29 children (40%). In total, hypercholaemia was a causative factor in 53 children (74%) with metabolic acidosis.

**Chloride**

Hypercholaemia was associated with reduced adrenaline requirement, in that 3 (4%) of hypercholaemic children received adrenaline, compared to 8 (28%) without hypercholaemia (p=0.005). However, there was no association between chloride elevation and increased CPB time (p=0.31), aortic cross-clamp time (p=0.68), predicted mortality (p=0.21), duration of inotrope requirement (p=0.90), mechanical ventilation (p=0.29), or PICU stay (p=0.17) (data not shown).

**Discussion**

The associations between cardiac surgical mortality, serious adverse events, and lactic acidosis in the immediate post-operative period have been well-documented[62-64, 66]. However, these studies reported mortality rates of 4 - 17%, whereas paediatric cardiac surgical mortality has since fallen to less than 2% in some centres[62-64, 66, 75]. Therefore, the lactic acidosis-outcome model might need to be reviewed in light of better post-operative survival, driven partly by general improvements in the outcome of paediatric intensive care and goal-directed treatment guidelines[75, 76].

This study showed that although metabolic acidosis is common following CPB, it is rarely due to elevation of lactate alone. Murray and colleagues have demonstrated, in a mixed group of 44 children following both open and closed cardiac surgery, that metabolic acidosis due to hyperlactatemia was rare, whereas elevation of ‘unmeasured’ anions was the most common cause of metabolic acidosis in their study population[51]. In a sub-group of children undergoing CPB, hypercholaemia was common, although the clinical significance of this abnormality was not clear[51]. Durward et al also showed, in children following CPB, that metabolic acidosis was most commonly due to either elevation of the strong ion gap or hypercholaemia[41]. It should also be acknowledged that all these studies, in common with routine clinical practice, tend to overestimate the true degree of metabolic acidosis and ‘unmeasured anions’ in younger infants, due to the use of adult reference ranges for bicarbonate by the arterial blood gas analyser to calculate base excess[17, 41, 50, 51].
The prognostic significance of acid-base data is difficult, if not impossible, to evaluate when cardiac surgical mortality is <2%. Therefore, given this unexpectedly low observed mortality rate, PICU mortality was not analysed as an endpoint. Instead, parameters such as duration of intensive care dependency were used as surrogate endpoints to denote adverse outcome. Despite the frequency of metabolic acidosis in this study, metabolic acidosis was not associated with severity of insult (duration of CPB or aortic cross-clamp time), risk of death, or longer duration of cardio-respiratory support in the PICU.

Hypoalbuminaemia is known to be associated with both prolonged ICU stay and mortality in critical illness[44, 77]. This study has demonstrated that hypoalbuminaemia is common in children following open cardiac surgery. Since pre-operative serum albumin data were not collected, it is not possible to determine whether this finding is a consequence of malnutrition, haemodilution on CPB, or an intra-operative acute phase response. Hypoalbuminaemia contributed a substantial positive component to the total base excess, an effect which might lead the clinician to underestimate the magnitude of an underlying metabolic acidosis. Given that hypoalbuminaemia, an alkalining factor, was associated with longer duration of both inotropic support and PICU stay, it is unsurprising that metabolic acidosis per se was not associated with these endpoints of adverse outcome[38, 45].

Hyperchloraemia was the most common cause of metabolic acidosis in these children and contributed a substantial negative component to the total base excess. Animal work has shown that saline resuscitation leading to hyperchloraemic acidosis is less effective than resuscitation with a balanced electrolyte colloid solution, but it is not clear whether these findings may be extrapolated to intrinsic, rather than extrinsic, hyperchloraemic acidosis[75]. The original hypothesis that post-operative hyperchloraemic metabolic acidosis is a benign phenomenon that might not require escalation of therapy is supported by the data, in that hyperchloraemia was not associated with longer CPB, aortic cross-clamp time, or duration of cardio-respiratory support. Moreover, children with hyperchloraemia were less likely to require adrenaline infusion for inotropic support on return from the operating theatre.
The origin of the excess chloride in these children may be the fluid used to prime the CPB circuit. Although the pump prime did not contain 0.9% saline, the classical intravenous fluid that causes hyperchloremia, the SHS colloid preparation contained chloride and sodium in a similar 1:1 ratio (130mmol/L), which would tend to narrow the strong ion difference and generate hyperchloremic metabolic acidosis[43, 71]. It is also possible that renal perfusion is impaired during CPB, even in the absence of regional tissue hypoxia, leading to acute tubular necrosis with chloride-sparing natriuresis[57, 67].

Although it is generally accepted that sodium bicarbonate therapy is not appropriate for lactic acidosis, a case might be made for sodium replacement in hyperchloremic acidosis, using sodium bicarbonate to lower the chloride:sodium ratio and increase the strong ion difference, rather than to replace bicarbonate in traditional terms[28, 79, 80]. However, in a haemodynamically stable post-operative patient, both renal impairment and the associated hyperchloremic acidosis might be expected to resolve spontaneously, without escalation of cardiac support. In this study, the lack of association between hyperchloremia and adverse endpoints, and the inverse association with adrenaline use, supports the view that hyperchloremic metabolic acidosis does not require active intervention. Whether these findings might be extrapolated to post-operative metabolic acidosis after other types of surgery is a matter for further investigation.

In contrast to the findings of Murray et al, no excess of 'unmeasured' anions was reflected by the strong ion gap in this patient population[51]. This finding may be due to a real absence of such anions, or the simultaneous presence of excess 'unmeasured' cations. The differences between the findings of this study and those of Murray might be ascribed partly to the fact that all of these patients underwent cardiopulmonary bypass[51, 71]. The duration of aortic cross-clamping during CPB was associated with statistically significant changes in lactate, corrected chloride, strong ion gap, and albumin. However, it should be acknowledged that these weak associations may not have clinical significance. It is also possible that such 'unmeasured' cations might be derived from the globulin-containing blood product used to prime the CPB circuit[61, 82]. However, Durward et al demonstrated not only that the strong ion gap was a common cause of metabolic acidosis after CPB, but that the strong ion gap was a good predictor of mortality following open cardiac surgery[41]. Whilst there may have been differences
in case mix between that patient population and our own, it is interesting to note that hyperchloraemia was also associated with survival in that study[41].

Mortality in this study group was only 1%. Patients were not pre-selected by diagnosis or surgical procedure at the time of enrolment, and the author believes that the study group is representative of children undergoing open cardiac surgery at the institution, for whom overall mortality was comparable at 2.4%. However, palliative surgery for hypoplastic left heart syndrome is not offered at this centre and more than 90% of patients fell into surgical risk categories 2 and 3[74]. Therefore, this patient group may have a different morbidity profile, and spectrum of acid-base derangement, from that of centres in which high-risk procedures form a larger proportion of the paediatric cardiac surgical workload.

Conclusion
Hyperchloraemia was the predominant acid-base abnormality, whereas primary hyperlactataemic and SIG-driven metabolic acidoses were rare, in this group of children with low predicted and observed mortality following open cardiac surgery.

The presence of a metabolic acidosis per se was not associated with prolonged intensive care dependency. By contrast, hypoalbuminaemia, an alkalising force, was associated with a prolonged requirement for inotropic support and intensive care stay.

Hyperchloraemia was associated with a reduced requirement for epinephrine infusion. Hyperchloraemia following cardiopulmonary bypass appears to be a benign phenomenon and it is suggested that hyperchloraemic metabolic acidosis should not prompt escalation of haemodynamic support.
Chapter 3
Lactate and the lactate:pyruvate ratio in children with post-operative cardiogenic shock

Introduction
In the previous chapter, it was shown that the principal metabolic acid-base disturbance in haemodynamically unstable children with low observed mortality following open cardiac surgery was hyperchloraemia, and the associations between hyperchloeraemia and ICU dependency were described. It remained to be seen whether hyperlactataemia, although mild and less frequent than hyperchloreaemia, might also have prognostic significance among these children; secondly, if hyperlactataemia were indeed associated with prolonged ICU dependency, whether the lactate:pyruvate ratio might provide additional prognostic value in this group of children.

Lactate is generated by the reaction of pyruvate with NADH, as a consequence of anaerobic glycolytic breakdown of glucose to pyruvate during oxygen-limited energy depletion (dysoxia) [13]. Since lactate requires either oxygen for re-conversion into pyruvate, or energy for conversion to glucose, excess lactate accumulates under anaerobic conditions [13]. However, lactate may also accumulate during accelerated aerobic glycolysis driven by epinephrine, or if renal and hepatic lactate clearance is reduced[13, 68]. Under these conditions, even transient increases in exogenous lactate delivery via red blood cell transfusions or cardiopulmonary bypass pump prime, might result in hyperlactataemia and trigger escalation of haemodynamic support[73, 75, 83-85]. It follows that mild lactic acidosis does not always signify regional tissue hypoxia or intraoperative oxygen debt[57-69].

Lactate and prognosis after cardiac surgery
Post-operative blood lactate levels are known to correlate with outcome after cardiac surgery in children and are associated with the rate of post-operative adverse events and PICU mortality[62-64, 66]. Based on these prognostic data, serial lactate levels have been incorporated into goal-directed therapeutic algorithms in the post-operative period [75, 76, 85].
Associations between cardiac surgical mortality, adverse events, and post-operative lactic acidosis were documented a decade ago among children with mortality rates of up to 17%[62-64, 66]. However, paediatric cardiac surgical mortality has since fallen to 5% or less in some centres[75, 76, 85]. Therefore, admission lactate measurement may no longer provide accurate prognostic data, particularly among patients with low mortality rates, and alternative markers of tissue dysxia and low cardiac output syndrome should be sought[41]. Unfortunately, measures of the magnitude of metabolic acidosis such as standard bicarbonate have limited value, due to the frequency of non-lactic metabolic acidosis caused by unmeasured anions, or hyperchloremia, as described in the previous chapter[41, 51, 64].

It is possible that the lactate:pyruvate ratio might be a more discriminating marker of occult tissue dysxia and morbidity following cardiopulmonary bypass, than the lactate level alone. The lactate:pyruvate ratio is a global marker of cytosolic redox potential, which may be elevated in both cardiogenic and septic shock, and is associated with early mortality[86-88]. The combination of elevated lactate and lactate:pyruvate ratio is also associated with increased mortality in critically ill adults[89]. However, these previous findings contrast with the early work of Weil and Aliffi, who found that the lactate:pyruvate ratio added no value to the lactate level in predicting survival from circulatory shock[3]. Therefore, the value of the lactate:pyruvate ratio for outcome prediction in patients with circulatory failure remains uncertain.

Aims

The investigations described in this chapter were designed to elucidate the relationships between metabolic acidosis, lactate, the lactate:pyruvate ratio, morbidity, and mortality, amongst children with post-operative cardiogenic shock. The prevalence of elevation of the lactate:pyruvate ratio, overall, among those children with and without metabolic acidosis, and among those children with and without hyperlactataemia, was to be determined; the associations between elevation of the lactate:pyruvate ratio and possible causative factors were to be explored; and finally, the associations between metabolic acidosis per se, hyperlactataemia, elevation of the lactate:pyruvate ratio, and ICU morbidity and mortality were to be analysed.
Materials and methods

Setting
The study was performed in the paediatric intensive care unit (PICU) of a university children's hospital, which is described in detail in Chapter 2, over a 1-year period from February 2003 to March 2004.

Patients
Children with post-operative cardiogenic shock were eligible for enrolment following surgical correction of congenital or acquired heart defects if they had undergone open cardiac surgery on cardiopulmonary bypass and required haemodynamic support, either in the form of inotrope infusion, or correction of intravascular volume depletion, at the time of admission to PICU. Eligible children were enrolled with the informed consent of a parent or guardian during the duty periods of the principal investigator (MH), and were not pre-selected on the basis of diagnosis or surgical complexity. The study was approved by the university research ethics committee and informed consent was obtained from a parent or guardian for participation. Patient demographics and cardiac diagnoses are presented in detail in the previous chapter.

Routine management
Blood and SHS were the fluids of choice for intra-operative volume resuscitation, in preference to 0.9% saline. Lactate-containing solutions, such as Ringer's lactate, were not used for intra-operative fluid resuscitation. Dopamine or dobutamine were the first line intra-operative inotropic agents of choice and epinephrine might be added for haemodynamically unstable patients with suspected low cardiac output. Post-operative PICU management might include the use of Ringer's lactate and alternative inotropic agents, such as the phosphodiesterase inhibitor milrinone, but these changes were made after admission blood sampling. The administration of sodium bicarbonate for correction of metabolic acidosis, whether due to hyperchloraemia or hyperlactataemia, was not recommended PICU practice at the time of the study.
**Blood sampling and data collection**

On admission to PICU, a single sample of arterial blood was immediately obtained from the indwelling cannula for arterial blood gas analysis and measurement of routine electrolytes, lactate and pyruvate. Arterial pH, pCO₂, standard bicarbonate, and standard base excess were measured and derived using a Radiometer ABL 520 blood gas analyser (Copenhagen, Denmark). Lactate was measured by the enzymatic method using a Beckman CX5 analyser (Berlin, Germany) with a within-assay coefficient of variation of 3% and total coefficient of variation of 4.3% (National Health Laboratory Service, Cape Town, South Africa). Strong ion difference and strong ion gap (SIG) were calculated from the routine electrolyte and acid-base data, as previously described [28, 29, 30, 32, 34, 49]. One mL of the same arterial blood specimen was immediately placed in a perchloric acid medium for protein denaturing, then placed in a freezer and stored at -80 degrees Celsius. Pyruvate samples were subsequently analysed in batches using high performance liquid chromatography (HPLC) with fluoresein detection, with a coefficient of variation of less than 15% (Ampath Laboratories, Pretoria, South Africa).

Thresholds for clinically significant biochemical derangements were defined a priori as standard bicarbonate < 22 mmol/L, lactate > 2 mmol/L, pyruvate > 0.1 mmol/L, and lactate:pyruvate ratio > 20 [41, 51, 90]. Aetiology of metabolic acidosis was assigned to hyperlactataemia (lactate > 2 mmol/L), hyperchloreaemia (corrected chloride > 110 mmol/L), strong ion gap (SIG > 2 mmol/L), or in the case of mixed acidosis, any combination thereof. Cardiac diagnoses, surgical procedures, duration of cardiopulmonary bypass, duration of aortic cross-clamp, Risk Adjustment in Congenital Heart Surgery (RACHS-1) categories, predicted risk of mortality (using Paediatric Index of Mortality 1), duration of mechanical ventilation, duration of inotropic support, and duration of PICU stay (expressed as calendar days, or part thereof), and observed PICU mortality, were recorded [2, 91].

**Statistical considerations**

Continuous data are reported as median (interquartile range; IQR) (range) and categorical data as n (%) with 95% confidence intervals (95% CI). In the crude analysis, non-parametric continuous data were analysed by the Mann-Whitney and Kruskal-Wallis
tests, and categorical data by the Fisher's Exact test, or the Chi-squared test for trend as appropriate, using Analyse-It statistical software (Analyse-It, UK).

In the multivariate analysis, the explanatory variables aortic cross-clamp time, cardiopulmonary time, cyanotic heart disease, and epinephrine infusion were entered, with lactate:pyruvate ratio as the outcome variable. Forward stepwise multiple linear regression was performed for the outcome variables duration of mechanical ventilation, duration of inotropic support, and duration of PICU stay, and the risk factors standard bicarbonate, lactate, and lactate:pyruvate ratio, using Stata version 8.2 statistical software (Statacorp, Texas, USA).

Results

Patients

A total of 278 paediatric cardiac surgical procedures were performed during the study period, with overall paediatric cardiac surgical mortality of 3.6% (n = 10). One hundred and sixty nine procedures were performed on cardiopulmonary bypass, with open cardiac surgical mortality of 2.4% (n = 4). Ninety seven of these children (57%) form the study group which is further described.

Demographic, clinical, and biochemical data are summarized in Table 3.1.
Table 3.1: Biochemical and clinical data, median, inter-quartile range (IQR), range.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>median</th>
<th>IQR</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>56</td>
<td>(19 – 95)</td>
<td>(0 – 166)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14</td>
<td>(9.1 – 22.6)</td>
<td>(2.1 – 50)</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>80</td>
<td>(60 – 115)</td>
<td>(17 – 232)</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>46</td>
<td>(27 – 65)</td>
<td>(0 – 149)</td>
</tr>
<tr>
<td>Risk of mortality (PIM)</td>
<td>0.02</td>
<td>(0.02 – 0.06)</td>
<td>(0.01 – 0.59)</td>
</tr>
<tr>
<td>pH</td>
<td>7.38</td>
<td>(7.32 – 7.430)</td>
<td>(7.17 – 7.61)</td>
</tr>
<tr>
<td>Standard bicarbonate (mEq/L)</td>
<td>20.1</td>
<td>(18.4 – 22)</td>
<td>(10.6 – 28.8)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.8</td>
<td>(1.3 – 2.5)</td>
<td>(0.7 – 9.1)</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.10</td>
<td>(0.07 – 0.15)</td>
<td>(0.04 – 0.39)</td>
</tr>
<tr>
<td>Lactate:pyruvate ratio</td>
<td>19</td>
<td>(14.6 – 22.5)</td>
<td>(5.4 – 38)</td>
</tr>
<tr>
<td>Mechanical ventilation (days)</td>
<td>2</td>
<td>(2 – 3)</td>
<td>(1 – 16)</td>
</tr>
<tr>
<td>Inotropic support (days)</td>
<td>3</td>
<td>(2 – 3)</td>
<td>(0 – 10)</td>
</tr>
<tr>
<td>PICU stay (days)</td>
<td>4</td>
<td>(3 – 4)</td>
<td>(2 – 20)</td>
</tr>
</tbody>
</table>

Ninety five children (98%) were receiving inotropic support on admission to PICU, of whom 11 (11%) received epinephrine by continuous infusion. Ninety-one patients (94%) fell into Risk Adjustment in Congenital Heart Surgery (RACHS-1) categories 2 or 3[74]. Median predicted mortality was 2% and there was a single nonsurvivor. Observed mortality in the study group (1%) was not significantly different from that among cardiopulmonary bypass patients overall (2.4%) (p = 0.44).

Operative risk categories
Cardiac surgical procedures are stratified according to modified RACHS-1 categories in Table 3.2 [74].
Table 3.2: Cardiac surgical procedures stratified by RACHS-1 risk categories. Data are median (IQR). *Denotes statistically significant differences at the 5% level.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>1 (n = 3)</th>
<th>2 (n = 46)</th>
<th>3 (n = 45)</th>
<th>4 - 6 (n = 3)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>34 (26 – 73)</td>
<td>66 (50 – 82)</td>
<td>101 (80 – 134)</td>
<td>131 (114 – 182)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>17 (13 – 35)</td>
<td>33 (20 – 51)</td>
<td>62 (44 – 87)</td>
<td>63 (51 – 76)</td>
<td>0.0002*</td>
</tr>
<tr>
<td>pH</td>
<td>7.4 (7.35 – 7.41)</td>
<td>7.39 (7.34 – 7.43)</td>
<td>7.38 (7.32 – 7.44)</td>
<td>7.42 (7.35 – 7.46)</td>
<td>0.89</td>
</tr>
<tr>
<td>Standard bicarbonate (mmol/L)</td>
<td>20 (20.9 – 21.2)</td>
<td>20.3 (19.5 – 22.3)</td>
<td>19.9 (18.3 – 21.6)</td>
<td>17.2 (16.4 – 21.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.9 (0.9 – 1.1)</td>
<td>1.8 (1.2 – 2.3)</td>
<td>2.0 (1.4 – 2.6)</td>
<td>5.1 (4.3 – 5.3)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.05 (0.05 – 0.07)</td>
<td>0.10 (0.07 – 0.14)</td>
<td>0.10 (0.07 – 0.15)</td>
<td>0.15 (0.15 – 0.27)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Lactate:pyruvate ratio</td>
<td>18.0 (15.7 – 18.0)</td>
<td>18.5 (14.7 – 22.0)</td>
<td>20.0 (15.0 – 23.0)</td>
<td>22.7 (18.4 – 28.3)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Children in higher categories of operative risk had higher admission levels of both lactate (p = 0.007) and pyruvate (p = 0.04). There was no significant increase in lactate:pyruvate ratio, nor was there a significant difference in admission pH (p = 0.89) or standard bicarbonate (p = 0.41) with increased operative risk category (data not shown).

Metabolic acidosis

On admission to PICU, 72 children (74%) demonstrated a metabolic acidosis, for which hypertactataemia was the single primary cause in only 1 child. In fact, the most common primary causes of metabolic acidosis were hyperchloraemia in 24 children (25%) and, to a lesser extent, elevated SIG in 9 children (9%). However, in the 38 children with mixed metabolic acidosis (39%), hypertactataemia constituted one of the causative factors in 28 children (29%), compared to hyperchloraemia in 29 children (30%). See Figure 3.1.
Figure 3.1: Children with metabolic acidosis, hyperlactataemia, and raised lactate:pyruvate ratio (LPR).
Data are n (%) and 95% confidence intervals (CI)

All
(n = 97)

Standard Bicarbonate < 22 mmol/L
(n = 72)
74% (CI 66 – 83)

Hyperlactataemia
(n = 29)
30% (CI 21 – 39)

Raised LPR
(n = 19)
20% (CI 12 – 27)

Normal LPR
(n = 10)
10% (CI 4 – 16)

No Hyperlactataemia
(n = 43)
44% (CI 34 – 54)

Standard Bicarbonate >= 22 mmol/L
(n = 25)
26% (CI 17 – 34)

Hyperlactataemia
(n = 12)
2% (CI 6 – 19)

Raised LPR
(n = 4)
4% (CI 0 – 8)

Normal LPR
(n = 8)
8% (CI 3 – 14)

No Hyperlactataemia
(n = 13)
13% (CI 7 – 20)

Raised LPR
(n = 2)
2% (CI 0 – 5)

Normal LPR
(n = 11)
11% (CI 5 – 18)
Figure 3.2: Lactate and pyruvate levels in 42 children with raised lactate:pyruvate ratio (LPR). Data are n (%) and 95% confidence intervals (CI)

- **Raised LPR**
  - (n = 42)
  - 43% (CI 33 – 54%)

- **Hyperlactataemia**
  - (n = 23)
  - 24% (CI 16 – 33%)

- **No Hyperlactataemia**
  - (n = 19)
  - 20% (CI 12 – 29%)

- **Raised Pyruvate**
  - (n = 5)
  - 8% (CI 2 – 12%)

- **Normal/Low Pyruvate**
  - (n = 18)
  - 19% (CI 11 – 28%)

- **Raised Pyruvate**
  - (n = 0)
  - 0% (CI 0 – 4%)

- **Normal/Low Pyruvate**
  - (n = 19)
  - 20% (CI 12 – 29%)
**Hyperlactataemia**

Hyperlactataemia occurred in 41 children (42%) and raised lactate:pyruvate ratio in 44 children (45%). The prevalence of raised lactate:pyruvate ratio among children with hyperlactataemia (56%) was similar to that in children with normal lactate (38%), (p=0.11). See Figure 3.1.

Raised admission lactate was associated with longer cardiopulmonary bypass time, median 98 min (IQR 20 – 232) vs 75 min (IQR 17 - 211) (p = 0.009), and an increased requirement for epinephrine infusion (24% vs 2%) (p = 0.0006).

**Raised lactate:pyruvate ratio**

Children with and without raised lactate:pyruvate ratio are compared in Table 3.3.
Table 3.3: Comparison of children with and without raised lactate:pyruvate ratio (LPR) in the immediate post-operative period. Data are median (IQR). *Denotes statistically significant differences at the 5% significance level.

<table>
<thead>
<tr>
<th></th>
<th>LPR &gt; 20 (n = 44)</th>
<th>LPR ≤ 20 (n = 53)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>94 (65 - 117)</td>
<td>80 (49 - 109)</td>
<td>0.23</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>53 (34 - 77)</td>
<td>38 (19 - 53)</td>
<td>0.01*</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (7.31 - 7.41)</td>
<td>7.39 (7.35 - 7.45)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Standard bicarbonate (mmol/L)</td>
<td>19.9 (18.2 - 21)</td>
<td>20.6 (18.8 - 23.10)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.1 (1.4 - 3.2)</td>
<td>1.8 (1.2 - 2.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.08 (0.06 - 0.14)</td>
<td>0.12 (0.09 - 0.15)</td>
<td>0.004*</td>
</tr>
<tr>
<td>LPR</td>
<td>27.8 (21.7 - 28.4)</td>
<td>15.0 (13.3 - 17.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>2 (2 - 3)</td>
<td>2 (2 - 3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Duration of inotropic support (days)</td>
<td>3 (2 - 4)</td>
<td>3 (2 - 3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Duration of PICU stay (days)</td>
<td>4 (3 - 5)</td>
<td>3 (3 - 4)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Raised lactate:pyruvate ratio was associated with longer aortic cross-clamp times (p = 0.01) and these children were also more likely to receive epinephrine by infusion (21% vs. 4%) (p = 0.02).

In the bivariate analysis, lactate:pyruvate ratio increased on average by 8.1 (95% CI 5.4 to 6.9) with each 1 mmol/L increase in lactate, and by 1.3 (95% CI 1.1 to 1.4) with each 0.01 mmol/L decrease in pyruvate. In the multivariate explanatory model, lactate:pyruvate ratio increased on average by 6.4 (95% CI 2.2 to 10.5) in children receiving epinephrine, and by 0.4 (95% CI 0.07 to 0.8) for every 10 minutes of aortic cross-clamp time, but there was no significant association between lactate:pyruvate ratio and duration of cardiopulmonary bypass (p = 0.82), or pre-existing cyanotic heart disease (p = 0.48), (data not shown).

**Raised lactate:pyruvate ratio in the presence of hyperlactataemia and metabolic acidosis**

Lactate:pyruvate ratio and other biochemical parameters are compared in children with and without hyperlactataemia and metabolic acidosis in Table 3.4. Lactate:pyruvate ratio and SIG were highest (p = 0.0025 and p = 0.023 respectively), and chloride lowest (p = 0.03), in those children with both hyperlactataemia and metabolic acidosis.
Table 3.4: Children with hyperlactataemia plus metabolic acidosis (n = 29), hyperlactataemia alone (n = 12), metabolic acidosis alone (n = 43), and without either hyperlactataemia or metabolic acidosis (n = 13). Data are median (IQR). * Denotes statistical significance at the 5% significance level.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>↑ Lactate ↓ SB</th>
<th>↑ Lactate Only</th>
<th>↓ SB Only</th>
<th>N lactate N/↑ SB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>53 (27 – 80)</td>
<td>50 (36 – 68)</td>
<td>45 (20 – 62)</td>
<td>34 (30 – 39)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>98 (77 – 135)</td>
<td>90 (68 – 140)</td>
<td>79 (48 – 110)</td>
<td>68 (50 – 84)</td>
<td>0.054</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (7.29 – 7.42)</td>
<td>7.47 (7.44 – 7.51)</td>
<td>7.36 (7.32 – 7.39)</td>
<td>7.44 (7.40 – 7.50)</td>
<td>–</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>4.6 (3.5 – 5.1)</td>
<td>4.1 (3.4 – 4.1)</td>
<td>4.5 (4.1 – 5.3)</td>
<td>4.2 (3.2 – 4.9)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Standard Bicarbonate (SB) (mmol/L)</td>
<td>18.8 (18.3 – 20.1)</td>
<td>23.7 (23.1 – 25.1)</td>
<td>19.8 (17.7 – 20.3)</td>
<td>23.1 (22.3 – 26.0)</td>
<td>–</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.7 (2.3 – 3.8)</td>
<td>2.9 (2.3 – 4.3)</td>
<td>1.3 (1.2 – 1.7)</td>
<td>1.2 (0.9 – 1.6)</td>
<td>–</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.15 (0.11 – 0.19)</td>
<td>0.16 (0.15 – 0.27)</td>
<td>0.08 (0.06 – 0.10)</td>
<td>0.09 (0.06 – 0.13)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Lactate:pyruvate ratio</td>
<td>22 (18 – 26)</td>
<td>17 (14 – 24)</td>
<td>19 (15 – 22)</td>
<td>15 (13 – 18)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138 (136 – 139)</td>
<td>139 (135 – 143)</td>
<td>138 (137 – 140)</td>
<td>139 (137 – 140)</td>
<td>0.77</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>109 (108 – 112)</td>
<td>110 (107 – 114)</td>
<td>112 (110 – 115)</td>
<td>110 (107 – 113)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Albumin (mmol/L)</td>
<td>26 (25 – 31)</td>
<td>30 (29 – 35)</td>
<td>30 (27 – 34)</td>
<td>31 (27 – 34)</td>
<td>0.067</td>
</tr>
<tr>
<td>SIG (mEq/L)</td>
<td>2.1 (-1.2 to 6.1)</td>
<td>-2.9 (-5.1 to -0.2)</td>
<td>1.1 (-1.7 to 4.5)</td>
<td>-1.6 (-4.2 to 1.8)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Mechanical ventilation (days)</td>
<td>2 (2 –3)</td>
<td>2 (2 – 4)</td>
<td>2 (2 – 3)</td>
<td>2 (2 – 3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Inotropic support (days)</td>
<td>3 (2 – 4)</td>
<td>3 (2 – 4)</td>
<td>3 (2 – 3)</td>
<td>2 (2 – 3)</td>
<td>0.54</td>
</tr>
<tr>
<td>PICU stay (days)</td>
<td>4 (3 – 6)</td>
<td>3 (3 – 5)</td>
<td>3 (3 – 4)</td>
<td>3 (3 – 4)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
**PICU morbidity**

Using simple linear regression, the admission lactate was associated with duration of mechanical ventilation \( (p = 0.0497) \), duration of inotropic support \( (p = 0.015) \), and duration of PICU stay \( (p = 0.01) \). None of these outcome variables were significantly associated with either standard bicarbonate, or the lactate:pyruvate ratio (data not shown).

Using forward stepwise multiple linear regression, of the risk factors standard bicarbonate, lactate, and lactate:pyruvate ratio, only lactate was independently associated with prolongation of PICU support. On average, duration of inotropic support increased by 0.29 days \( (95\% \text{ CI } 0.06 - 0.52) \), duration of mechanical ventilation increased by 0.27 days \( (95\% \text{ CI } 0.0004 - 0.56) \), and duration of PICU stay increased by 0.42 days \( (95\% \text{ CI } 0.10 - 0.74) \) for each 1 mmol/L increase in admission lactate.

**Discussion**

This chapter describes the relationships between admission lactate:pyruvate ratio, lactate, and morbidity, in a group of children characterized by predominantly hyperchloreaemic metabolic acidosis, low-moderate RACHS-1 operative risk categories, and predicted PICU mortality of less than 5%\(^2,\) \(^91\). Since observed post-operative mortality was negligible, surrogate markers of operative morbidity, such as duration of mechanical ventilation, inotropic support, and PICU stay, were selected for evaluation.

The patient group was characterized by only mild-moderate metabolic acidosis and hyperlactataemia at the time of admission to PICU, yet derangement of the lactate:pyruvate ratio was frequent. Almost half of the children had clinically significant hyperlactataemia, or elevated lactate:pyruvate ratio, and almost a quarter of children had elevation of both lactate and lactate:pyruvate ratio simultaneously. Similarly, three quarters of children demonstrated a metabolic acidosis in the immediate post-operative period (see Figure 1) and, as might be expected, a higher proportion of children with metabolic acidosis had raised lactate levels. Although hyperlactataemia was an infrequent primary cause of metabolic acidosis, since most primary metabolic acidosis was due either to hyperchloreaemia or elevated SIG, as described in the previous chapter, a large proportion of mixed metabolic acidosis was due in part to hyperlactataemia. It is also striking that many children with elevation of lactate did not
have a metabolic acidosis, which may be attributed to co-existing alkalotic forces such as hypoalbuminaemia[33]. The presence of respiratory alkalosis might have contributed directly to hyperlactataemia, due to inhibition of lactate clearance[92].

Almost half of the children with elevated lactate:pyruvate ratio demonstrated elevated lactate and normal, or low, pyruvate, consistent with anaerobic glycolysis. It should also be noted that many children with elevated lactate:pyruvate ratio did not have hyperlactataemia. In these children, elevation of the lactate:pyruvate ratio was due not to increased lactate, but to lower pyruvate. The clinical significance of this finding is not clear, but abnormal lactate:pyruvate ratios with normal lactate levels, suggesting pyruvate utilization, have been noted previously in children with septic shock[93]. The third group of importance comprises children with hyperlactataemia, but with a normal lactate:pyruvate ratio due to simultaneously elevated pyruvate. The apparent discordance between elevation of lactate and the lactate:pyruvate ratio in these children might arise from a combination of epinephrine-driven aerobic glycolysis (hyperlactataemia with normal lactate:pyruvate ratio), anaerobic glycolysis due to cellular dysoxia (hyperlactataemia with raised lactate:pyruvate ratio), or depressed glycolysis (normal lactate with raised lactate:pyruvate ratio), occurring at different rates, in different tissues[13, 86].

Hyperlactataemia was associated with longer operative cardiopulmonary bypass time; elevated lactate:pyruvate ratio was associated with longer aortic cross-clamp time; and both hyperlactataemia and elevated lactate:pyruvate ratio were associated with use of epinephrine infusion. It might have been expected that the lactate:pyruvate ratio would rise with longer periods of ischaemia related to aortic cross-clamping, and even the last finding is not entirely surprising, since epinephrine has previously been shown to increase both lactate and lactate:pyruvate ratio[86]. However, it should be noted that the increase in lactate:pyruvate ratio in that study was in the context of septic shock, resistant to dopamine therapy, and that the use of epinephrine caused gastric mucosal acidosis as well as a raised lactate:pyruvate ratio[86]. The inference from that finding is that the adverse haemodynamic profile of epinephrine caused local hepatoesplanchnic hypoxia-lachaemia, leading to a raised lactate with a raised lactate:pyruvate ratio[86].

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It might also be expected that both admission lactate and lactate:pyruvate ratio would increase with higher RACHS-1 categories (see Table 3), but this was not the case[91]. In the multivariate analysis, hyperactataemia was associated with longer duration of inotropic support, mechanical ventilation, and PICU stay, even among children with relatively low operative risk and low post-operative mortality. It appears that the admission lactate level remains a useful prognostic marker of morbidity following open cardiac surgery in children with relatively mild metabolic acidosis. However, metabolic acidosis per se was not a useful marker of post-operative outcome[64].

It has been suggested that the lactate:pyruvate ratio might distinguish patients with occult tissue dysoxia, from those with hyperactataemia due to aerobic glycolysis, on the basis of markers of PICU morbidity[73, 83, 84]. However, as noted above, raised lactate:pyruvate ratio was associated not only with elevated lactate, but with lower pyruvate levels, suggesting accelerated pyruvate utilisation. Secondly, elevation of the lactate:pyruvate ratio was not associated with prolongation of PICU stay, mechanical ventilation, or inotropic support. This finding is in agreement with Weil et al., who demonstrated that elevated lactate:pyruvate ratio was a poor additional prognostic indicator, compared to lactate alone, in human circulatory shock[3]. It can be seen that the lactate:pyruvate ratio would be a poor marker of tissue hypoxia if the anaerobic threshold were variable in different organ systems, and if both oxidative and anaerobic glycolytic energy production proceeded independently in separate tissue compartments[13, 68]. It is also likely that the timing of blood sampling confounds interpretation of the lactate:pyruvate ratio. Well and Affili demonstrated in an animal model of haemorrhagic shock that pyruvate rose promptly, whereas the rise in lactate was slower, but sustained, leading to delayed elevation of the lactate:pyruvate ratio[3]. Determination of serial intra- and post-operative lactate:pyruvate ratios, in conjunction with mixed venous oxygen saturation, would be required to clarify this question. It is a limitation of this study that mixed venous oxygen saturation and cardiac output data are not available for review in conjunction with the acid-base parameters.

The principal limitations for interpretation of the study findings arise from the relatively low pre-operative risk and low post-operative mortality rate that was observed in the study group. Since patients were not pre-selected on the basis of surgical procedure or severity of illness, and because the mortality rate was similar to that of all children who
underwent cardiopulmonary bypass, the author believes that the study group accurately reflects children undergoing open cardiac surgery at this centre, where higher risk procedures (RACHS-1 categories 4 to 6) are performed less frequently due to resource limitations[91]. It follows that these findings should not be extrapolated directly to high volume cardiac surgical centres where procedures in high operative risk categories are performed routinely, since the incidence of severe hyperlactataemia and metabolic acidosis, and the PICU mortality rate, may be higher[74]. Future research should examine the relationship between serial lactate:pyruvate ratios and objective measures of tissue hypoxia or hypoperfusion in selected high risk surgical categories.

Nevertheless, these data provide an indication that measurement of the lactate:pyruvate ratio in children with mild-moderate metabolic acidosis would not add useful prognostic information to that derived from routine operative risk data, including the post-operative lactate level alone. Given that pyruvate analysis requires specialised sample processing (in a perchloric acid medium) and laboratory techniques, routine measurement of pyruvate would not be warranted.

Conclusion
In summary, elevation of the lactate:pyruvate ratio was common in this group of children with mild-moderate, predominantly hyperchloaemic metabolic acidosis, who also had low mortality associated with post-operative cardiogenic shock following open cardiac surgery. Raised lactate:pyruvate ratio was more frequent in children with metabolic acidosis, yet it occurred commonly in children without hyperlactataemia, since elevation of the lactate:pyruvate ratio was due partly to lower pyruvate.

Children with raised lactate:pyruvate ratio had longer aortic cross-clamp times and were more likely to receive epinephrine by infusion. However, it was hyperlactataemia, rather than elevation of the lactate:pyruvate ratio, or metabolic acidosis, that was associated with prolongation of inotropic support, mechanical ventilation, and PICU stay. Analysis of pyruvate and calculation of lactate:pyruvate ratios did not add useful prognostic information in this clinical setting. These findings should be tested in tandem with measures of regional and global hypoperfusion, and in centres with a larger proportion of cardiac surgical procedures in higher operative risk categories.
Chapter 4
Metabolic acidosis and outcome in children with septic shock

Introduction:
Sepsis and septic shock
The majority of studies of prognostic factors in severe sepsis and septic shock have focused on the associations between lactate and outcome [3, 16, 49, 93-99]. For example, the ground-breaking work of Weil and colleagues demonstrated lactate was the best discriminator of survivors and nonsurvivors in patients with shock[3]. Bakker et al showed in adults that lactate measurement was superior to measurement of oxygen delivery and consumption variables for prediction of mortality in septic shock, and that the duration of lactic acidosis, as measured by serial lactate levels, was the best predictor of multiple organ failure and survival[16, 94]. In a study of adults with severe sepsis, Friedman reported that although admission lactate levels did not differ between survivors and nonsurvivors, lactate levels remained high in ICU nonsurvivors, but progressively decreased in survivors[95]. Again, in this study, lactate was a better predictor of outcome than oxygen delivery or consumption variables[95]. These findings are important, since they provide an indication that the association between lactate and outcome is founded, at least in part, on a mechanism other than global hypoxia-ischaemia[16, 94, 95].

However, regardless of the underlying reason for elevation of the lactate level, the association between hyperlactataemia and poor prognosis in sepsis and septic shock is described repeatedly in the adult critical care literature. Trzeciak and co-workers demonstrated that an admission lactate > 4 mmol/L was associated with 8-fold higher odds of death within three days, among adults with sepsis[99]. Similarly, Shapiro reported that a lactate level > 4 mmol/L was 92% specific for prediction of death among adults presenting to the emergency department with sepsis[98]. Day and colleagues showed that admission hyperlactataemia was associated with fatal outcome in adults with severe malaria[96]. Levy et al reported that among 60 adults with septic shock, those patients who died within 24 hours had a higher admission lactate, and that although initial lactate levels were not different overall between survivors and nonsurvivors, the duration of lactic acidosis was associated with multi-organ failure and mortality[97]. Further underlining the importance of duration of hyperlactataemia, Nguyen showed in adults with severe sepsis and septic shock that those patients with greater clearance of lactate within the first 6 hours of admission
had improved survival[97]. Lastly, in a large study of 111 adults with septic shock, the admission lactate level, along with the admission mean arterial pressure, was independently associated with 30-day mortality[100]. The importance of the use of prognostic markers such as lactate in severe sepsis, is underscored by the findings of Nguyen et al, who demonstrated that if lactate monitoring was completed as part of a bundle of quality indicators for the early management of severe sepsis and septic shock in adults, the odds of in-hospital mortality were decreased[101].

**Pediatric studies**

Comparatively, few studies have investigated the prognostic value of acid-base variables in children with septic shock[49, 93, 102]. In a study of 31 children with severe sepsis, Duke and colleagues reported that although the admission lactate level was not discriminatory, a lactate level > 3 mmol/L at 12 and 24 hours was predictive of ICU mortality[102]. Duges has also demonstrated in a small group of children with septic shock, none of whom died, that normalisation of bicarbonate and lactate levels paralleled clinical recovery[93]. The author has previously demonstrated in a preliminary study of children with shock of heterogeneous aetiology, including sepsis, that the magnitude of a metabolic acidosis, as measured by the admission base excess, had no predictive value for PICU mortality; secondly, that the level of 'unmeasured' anions inferred from the strong ion gap was also not predictive of mortality; thirdly, that hyperchloremia was associated with a trend towards PICU survival; and lastly, that the admission lactate level was the best predictor of PICU outcome, with an area under the ROC curve of 0.83, which was equivalent to that of the PIM I score (0.71)[49]. However, these findings might not be generalised to other settings, since the study sample was small, the study included children with shock due to causes other than sepsis, and the effect of potential confounding variables on the associations with outcome were not examined[49].

**Aims**

The aims of this study were, firstly, to describe the relationships between admission metabolic acidosis, the components of that metabolic acidosis, with particular emphasis on lactate, and measures of intensive care outcome - including the duration of inotropic support, duration of mechanical ventilatory support, duration of intensive care admission, and duration of intensive care unit survival; and secondly, to develop a multivariate predictive model for ICU survival, based on admission acid-base parameters, and adjusted for potential confounding factors.
Materials and methods

Setting

This prospective study was performed in the paediatric intensive care unit (PICU) of a university children's hospital over the 2-year period from February 2003 to March 2005. The study setting is described in detail in previous chapters. Children with septic shock are admitted to the PICU directly from the children's hospital emergency department and in-patient wards, as well as via paramedic transfer, after stabilization, from local district and other regional centres.

Patients

Children with septic shock would usually only be referred to PICU if initial emergency department resuscitation to correct a pre-existing intravascular volume depletion, usually 30 - 50 ml/kg of intravenous fluid boluses, was unsuccessful. All children with a clinical diagnosis of septic shock who required haemodynamic support, defined as either intravascular volume replacement or inotropic support, at the time of admission to PICU were eligible for enrolment. A clinical diagnosis of septic shock was made in the presence of either hypotension for age, or prolonged capillary refill time (≥ 5 seconds), which was responsive to inotropic infusion or fluid correction of intravascular volume depletion, in the presence of acute mental changes, hypoxaemia, or oliguria, plus hyperthermia or hypothermia, tachycardia, tachypnoea, and either an abnormal total leucocyte count, abnormal neutrophil fraction, or elevated procalcitonin level[103]. Laboratory confirmation of microbial infection was not required in order to assign a clinical diagnosis of septic shock[103]. The study was approved by the university research ethics committee; eligible children were enrolled with the informed consent of a parent or guardian during the duty periods of the principal investigator and were not pre-selected on the basis of diagnosis or severity of illness.

Routine management of septic shock

Lactate-containing solutions, such as Ringer's lactate, were the resuscitation fluids of choice for repletion of intravascular volume in shock, both before and during PICU admission. Normal (0.9%) saline was rarely used for treatment of septic shock. Adequacy of intravascular volume therapy was judged on the basis of subjective clinical parameters (such as capillary refill time, palpation of distal pulses, and palpation of the hepatic margin) and continuous invasive pressure monitoring (central venous and mean blood pressures). Measurements of cardiac output were not
routinely performed. Admission acid-base parameters, such as the base excess and lactate, might also have contributed to PICU fluid or inotrope management decisions, but only after study samples had been taken. The administration of sodium bicarbonate for correction of metabolic acidosis, whether due to hyperchloremia or hyperlactataemia, was not recommended PICU practice at the time of the study. Dopamine or dobutamine were the first line inotropic agents of choice. Epinephrine or norepinephrine might be added for refractory hypotension despite adequate fluid therapy. PICU management might also include the use of alternative inotropic agents, such as the phosphodiesterase inhibitor milrinone, but all these changes would usually be made after admission blood sampling.

**Blood sampling and data collection**

Immediately on admission to PICU, a single sample of arterial blood was obtained from the indwelling cannula for arterial blood gas (ABG) analysis and measurement of routine electrolytes and lactate. Arterial pH, pCO₂, bicarbonate, standard base excess (BE), and lactate, were measured and derived using a Radiometer ABL 520 blood gas analyser (Copenhagen, Denmark). As in the previous study of post-operative cardiogenic shock, reference values for bicarbonate used by the Radiometer ABL 520 blood gas analyser are based on adult norms. Serum electrolytes (sodium, potassium, calcium, magnesium, phosphate) were measured by the ion-specific electrode method using a Beckman CX9 Pro analyser (Berlin, Germany). Serum albumin was measured by the reagent method using a Beckman CX9 Pro analyser (Berlin, Germany).

Strong ion difference and strong ion gap (SIG) were calculated from the laboratory electrolyte and acid-base data, using the standard formulae, as previously described[32, 34, 49]. Briefly, a Fenn-Stewart approach, with the modifications of Figge, was used to derive calculated strong ion difference (SIDc), effective strong ion difference (SIDE), and strong ion gap (SIG)[26, 29, 30, 32, 34, 104]. Chloride was corrected for free water (cCl), i.e. to a serum sodium of 140 mmol/L, by multiplying the measured chloride:sodium ratio by a factor of 140[32, 49]. Thresholds for clinically significant biochemical derangements were defined *a priori* as albumin < 30 g/L, chloride > 110 mmol/L, lactate > 2 mmol/L, and SIG > 2 mmol/L[49, 90, 105, 106]. Metabolic acidosis was defined as standard bicarbonate (SB) < 22 mmol/L. Aetiology of metabolic acidosis was assigned *a priori* to hyperlactatemia (lactate > 2 mmol/L), hyperchloremia (corrected chloride > 110 mmol/L), strong ion gap (SIG > 2 mmol/L), or in the case of mixed acidosis, any combination thereof, as described in chapter 2.
**Partitioned base excess approach**

The individual components of the standard base excess (BE) contributed by albumin (BE alb), free water (BE fw), chloride (BE cl), and lactate (BE lact), were calculated using the equations of Griffix, incorporating normal values for the ion-sensitive electrode method[32, 57, 58]. For the purposes of these calculations, median reference values were taken as albumin 42 g/L, sodium 140 mmol/L, chloride 108 mmol/L, and lactate 1.5 mmol/L[57, 58]. See chapter 2 for equations[32].

Clinical diagnoses, underlying or pre-existing conditions, predicted risk of mortality (Paediatric Index of Mortality 1 during the study period), duration of mechanical ventilation, duration of inotropic support, and duration of PICU stay (expressed as calendar days, or part thereof), and observed PICU mortality, were recorded[2]. Since it was expected that this patient population might have a relatively high PICU mortality, Day-28 ‘alive and ventilator-free’, ‘inotrope-free’, and ‘ICU-free’ days, were calculated from the number of days (or parts thereof) in which the patient was both alive, and not requiring the specified ICU support, within the period from PICU admission until 28 days thereafter.

**Statistical considerations**

Data are reported as median (interquartile range; IQR), with or without (range) as necessary; n (%); and 95% confidence intervals (95% CI). In the crude analysis, non-parametric continuous data were analysed by the Mann-Whitney and Kruskal-Wallis tests, and categorical data by the Fisher’s Exact test or the Chi-squared test for trend as appropriate, using Analyse-It statistical software (Analyse-It, UK).

In the bivariate analyses, logistic regression was performed using the categorical outcome variable survival, and the explanatory variables, age, weight, epinephrine infusion, and admission pH, standard bicarbonate, base excess, lactate, sodium, potassium, corrected chloride, calcium, magnesium, phosphate, albumin, and strong ion gap.

In the multivariate analysis, a forward (non-automated) logistic regression model was developed using the outcome variable survival and explanatory variables selected on the basis of clinical interest, and on the basis of statistical significance of the association in the preceding bivariate analysis. Similarly, linear regression models were developed for the continuous outcome variables Day-28 ventilator-free, inotrope-free, and ICU-free days, and the explanatory variables listed above.
Bivariate and multivariate regression analyses were performed using Intercooled Stata version 8.2 statistical software (Statacorp, Texas, USA).

Results
Eighty-three children with a clinical diagnosis of septic shock were enrolled. Median age was 4.8 months (IQR 4.4 – 8.5) and median weight 6.5 kg (IQR 4.5 – 9.0). Seventy-six children (92%) were mechanically ventilated and 10 children (12%) were receiving epinephrine, at the time of admission to PICU. Median predicted PICU mortality (PIM 1) was 0.30 (IQR 0.12 – 0.50) and there were 27 nonsurvivors (33%), yielding a standardized mortality ratio of 1.10. Median duration of PICU stay in survivors was 5 days (IQR 4 – 8) (range 1 – 24) and time to death in nonsurvivors was 2 days (IQR 1 – 4) (range 2 – 20). Median Day-28 alive and ventilator-free days were 23 (IQR 0 – 25), inotrope-free days 25 (IQR 0 – 27), and ICU-free days 20 (IQR 0 – 24). The underlying condition or septic focus was identified in 52 of the 83 children (63%). See Table 4.1 below.
<table>
<thead>
<tr>
<th>Identified underlying condition</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>17</td>
<td>21%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>13</td>
<td>16%</td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td>Group B beta haemolytic Streptococcal sepsis</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>8%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Septic burn wounds</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Klebsiella septicemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intussusception</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Underlying condition not identified</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock, unidentified focus</td>
<td>31</td>
<td>37%</td>
</tr>
</tbody>
</table>
Biochemical and acid-base data

This group of children demonstrated severe acidaemia, with almost 25% having admission pH less than 7.0 (see Table 4.2 below). The group also demonstrated a severe metabolic acidoia, with more than 50% having admission standard bicarbonate less than 12 mmol/L. Overall, this metabolic acidoia was accompanied by moderate hypertactataemia, with almost 25% of children having admission lactate greater than 10 mmol/L, as well as moderate hyperchloreaemia (median CI 115 mmol/L), mild elevation of strong ion gap (median 3.1 mEq/L), and severe hypoalbuminaemia (median 20 g/L).

Table 4.2: Admission biochemical and acid-base data (n = 83).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>IQR</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.19</td>
<td>7.03</td>
<td>7.36</td>
</tr>
<tr>
<td>SB (mmol/L)</td>
<td>11.9</td>
<td>9.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>4.8</td>
<td>2.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>136</td>
<td>132</td>
<td>144</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>111</td>
<td>107</td>
<td>121</td>
</tr>
<tr>
<td>Corrected Chloride (mmol/L)</td>
<td>115</td>
<td>111</td>
<td>120</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>20</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>Strong ion gap (mEq/L)</td>
<td>3.1</td>
<td>0.7</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Base excess (BE)

Median net base excess was very low (-16 mEq/L) (see Table 5) and almost 75% of children demonstrated an admission net base excess lower than -10 mEq/L. The major positive component was contributed by albumin (median 5.4 mEq/L) and the major negative components were contributed by chloride (median -7.5 mEq/L), and the 'unmeasured' anions estimated from the base excess gap (median -6.3 mEq/L), and lactate (median -3.3 mEq/L).
Table 4.3: Partitioned base excess (BE) (n = 83).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>IQR</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net BE (mEq/L)</td>
<td>-16.0</td>
<td>-19.4</td>
<td>-29.9</td>
</tr>
<tr>
<td>Albumin BE (mEq/L)</td>
<td>5.4</td>
<td>4.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Free Water BE (mEq/L)</td>
<td>-1.2</td>
<td>-2.6</td>
<td>-7.2</td>
</tr>
<tr>
<td>Chloride BE (mEq/L)</td>
<td>-7.5</td>
<td>-12.2</td>
<td>-20.6</td>
</tr>
<tr>
<td>Lactate BE (mEq/L)</td>
<td>-3.3</td>
<td>-8.8</td>
<td>-20.5</td>
</tr>
<tr>
<td>Base excess gap (mEq/L)</td>
<td>-6.3</td>
<td>-10.4</td>
<td>-21.9</td>
</tr>
</tbody>
</table>

Metabolic acidosis

Seventy-nine children (95%) demonstrated a metabolic acidosis on admission to PICU (see Table 4.4). This metabolic acidosis was mixed in 65 children (82%), with hyperlactataemia-hyperchloraemia-strong ion gap acidosis occurring most commonly (38%), followed by hyperlactataemia-hyperchloraemia (23%). In 14 children (18%), metabolic acidosis was due to a single primary cause, the most common of which was hyperchloraemia (11%). Hyperlactataemia was the single primary cause of the metabolic acidosis in only 3 children (4%). Overall, hyperchloraemia (82%) and hyperlactataemia (76%) were the most frequent individual underlying causes of metabolic acidosis.
Table 4.4:
Underlying cause/s of metabolic acidosis (n = 79).

<table>
<thead>
<tr>
<th>Underlying cause/s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Lactate ↑ Chloride ↑ SIG</td>
<td>n = 30 (38%)</td>
</tr>
<tr>
<td>↑ Lactate ↑ Chloride</td>
<td>n = 18 (23%)</td>
</tr>
<tr>
<td>↑ Lactate ↑ SIG</td>
<td>n = 9 (11%)</td>
</tr>
<tr>
<td>↑ Lactate ↑ Chloride ↑ SIG</td>
<td>n = 3 (4%)</td>
</tr>
<tr>
<td>↑ Chloride ↑ SIG</td>
<td>n = 8 (10%)</td>
</tr>
<tr>
<td>↑ Chloride ↑ SIG</td>
<td>n = 9 (11%)</td>
</tr>
<tr>
<td>↑ SIG</td>
<td>n = 2 (3%)</td>
</tr>
</tbody>
</table>

↑ Lactate Subtotal | n = 69 (76%)
↑ Chloride Subtotal | n = 65 (82%)
↑ SIG Subtotal | n = 49 (62%)

Total | n = 79 (100%)

Outcome
In the crude analysis, before correcting for multiple comparisons, nonsurvivors demonstrated significantly lower median admission base excess (-19.3 vs -15.0 mEq/L), higher lactate (8.1 vs 3.2 mmol/L), and lower albumin (16 vs 22 g/L), as well as higher predicted risk of mortality (0.44 vs 0.24), compared to survivors (see Table 4.5 below). Admission pH (p = 0.20), corrected chloride (p = 0.78), and strong ion gap (p = 0.72), were similar between survivors and nonsurvivors. Receiver operating characteristic (ROC) curves were constructed to demonstrate sensitivity and 1-specificity of the admission acid-base variables for prediction of mortality.
Table 4.5: Survivors (n = 56) and Nonsurvivors (n = 27). Data are median (IQR) (range) and n (%). * Statistically significant differences.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivor Median</th>
<th>Nonsurvivor Median</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>4.8 (4.4-8.3)</td>
<td>4.8 (4.3-9.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>6.4 (4.7-9.0)</td>
<td>6.8 (3.9-9.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>PIM predicted risk of mortality</td>
<td>0.24 (0.12-0.43)</td>
<td>0.44 (0.2-0.6)</td>
<td>0.02*</td>
</tr>
<tr>
<td>pH</td>
<td>7.21 (7.08-7.35)</td>
<td>7.15 (6.9-7.37)</td>
<td>0.20</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>3.9 (2.9-5.2)</td>
<td>3.9 (3.1-5.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>-15.0 (-18.1 to -9.5)</td>
<td>-19.3 (-23.6 to -10.3)</td>
<td>0.034*</td>
</tr>
<tr>
<td>SB (mmol/L)</td>
<td>12.4 (10.2-16.8)</td>
<td>9.6 (7.4-15.3)</td>
<td>0.051</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>9.3 (7.7-10.2)</td>
<td>7.9 (6.4-11.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.2 (1.8-7.4)</td>
<td>8.1 (5.2-15.4)</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Corrected Chloride (mmol/L)</td>
<td>116 (112-120)</td>
<td>115 (111-122)</td>
<td>0.78</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.8 (2.0-4.9)</td>
<td>4.8 (3.6-6.0)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>22 (18-28)</td>
<td>16 (12-18)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>Strong ion gap (mEq/L)</td>
<td>3.4 (0.7 to 6.7)</td>
<td>2.9 (1.8 to 5.9)</td>
<td>0.72</td>
</tr>
<tr>
<td>Epinephrine infusion</td>
<td>5 (9%)</td>
<td>5 (19%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>50 (90%)</td>
<td>26 (96%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>53 (95%)</td>
<td>26 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>↑ Lactate</td>
<td>37 (88%)</td>
<td>26 (96%)</td>
<td>0.003*</td>
</tr>
<tr>
<td>↑ Chloride</td>
<td>45 (80%)</td>
<td>21 (78%)</td>
<td>1.00</td>
</tr>
<tr>
<td>↑ Strong ion gap</td>
<td>33 (59%)</td>
<td>19 (70%)</td>
<td>0.45</td>
</tr>
<tr>
<td>↓ Albumin</td>
<td>48 (86%)</td>
<td>26 (96%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Figure 4.1: Comparison of lactate, cChloride, and strong ion gap receiver operating characteristic (ROC) curves for prediction of outcome

Area under the survival prediction curve was 0.75 for lactate (95% CI 0.64 – 0.86), but only 0.52 (95% CI 0.38 – 0.66) for cChloride and 0.52 (95% CI 0.39 – 0.66) for strong ion gap, i.e. not statistically different from the area under the line of non-discrimination.

Figure 4.2: Comparison of lactate and PIM I predicted outcome
Change at the 5% significance level.

Examine the change in each of the individual explanatory variables by their effect on survival rate. The proportion of the variance explained by each variable is 1.0%. The model with a decreased odds ratio for survival of 0.63, and each 1% model increase in postpartum with a decreased odds ratio for each 1% model increase in lactase was associated with a decreased odds ratio for each 1% model increase in lactase was associated with an increased odds ratio for survival of 1.4. By contrast, increase in lactase with an increased odds ratio for survival of 1.07, and each 1% were associated with an increased odds ratio for survival. Each 1% model increase in postpartum increase in lactase and postpartum was significantly associated with survival whereas increase in lactase and postpartum were

The area under the ROC curve was 0.74 (95% CI 0.63 - 0.86), but the area

![Graph](image-url)

Figure A.3: Comparison of standard binomial, censored, and survival.

From each other:

outcome (0.66 with 95% CI 0.53 - 0.79) ROC curves were not significantly different.

The area under the ROC curve (0.75 with 95% CI 0.64 - 0.86) and PM I predicted.
Table 4.6: Unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) for survival. *Denotes statistical significance at the 5% significance level.

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>OR</th>
<th>95% CI</th>
<th>Pseudo-R-Squared</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>0.99</td>
<td>0.97 1.02</td>
<td>0.05</td>
<td>0.60</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.99</td>
<td>0.90 1.10</td>
<td>0.01</td>
<td>0.89</td>
</tr>
<tr>
<td>Epinephrine infusion (Y/N)</td>
<td>0.43</td>
<td>0.11 1.64</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>pH</td>
<td>6.69</td>
<td>0.77 58.3</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>0.99</td>
<td>0.79 1.25</td>
<td>0.03</td>
<td>0.94</td>
</tr>
<tr>
<td>SB (mmol/L)</td>
<td>1.08</td>
<td>0.98 1.20</td>
<td>0.001</td>
<td>0.74</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>1.07</td>
<td>1.01 1.15</td>
<td>0.0001</td>
<td>0.048*</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>0.88</td>
<td>0.50 0.88</td>
<td>0.0001</td>
<td>0.005*</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.83</td>
<td>0.75 0.92</td>
<td>0.09</td>
<td>0.0001*</td>
</tr>
<tr>
<td>cChloride (mmol/L)</td>
<td>1.00</td>
<td>0.93 1.07</td>
<td>0.003</td>
<td>0.92</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>1.14</td>
<td>1.05 1.24</td>
<td>0.02</td>
<td>0.001*</td>
</tr>
<tr>
<td>Strong ion gap (mEq/L)</td>
<td>1.04</td>
<td>0.95 1.14</td>
<td>0.003</td>
<td>0.38</td>
</tr>
</tbody>
</table>
**Multivariate logistic regression model: PICU Survival**

Although changes in weight were not associated with increased or decreased odds of survival *per se*, weight was included in the final multivariate regression model because of the significant confounding effect of the variable weight on associations with co-variables.

By contrast, admission base excess and standard bicarbonate were not significant predictors of outcome after adjustment for weight and the other biochemical parameters [base excess odds ratio for survival = 1.14 (95% CI 0.80 - 1.63) and standard bicarbonate odds ratio for survival = 0.79 (95% 0.44 - 1.40)]. Model fit worsened when base excess and standard bicarbonate were included, and since these are both dependent variables according to Stewart theory, correlating with corrected chloride with $R = -0.30$ and $R = -0.37$ respectively, base excess and standard bicarbonate were not included in the final predictive model. Although the effect of corrected chloride on survival was not statistically significant in the bivariate analysis, corrected chloride was included in the final model, because its effect became significant at the 5% level - after adjustment for weight and the other biochemical parameters.

Epinephrine usage and strong ion gap were also excluded from the multivariate model, because of a lack of statistically significant adjusted effects on survival, and worsened fit of the regression model when these variables were included.

The final multivariate logistic regression model was of the form:

\[
\text{Log Odds of Survival} = 15.5 - (0.11 \times \text{Weight}) - (0.17 \times \text{Lactate}) - (0.42 \times \text{Potassium}) - (0.11 \times \text{cChloride}) + (0.11 \times \text{Albumin})
\]

This final model explained approximately 29% of the variability in outcome (Pseudo-R-Squared = 0.29) and was not significantly different from the optimal fitted model (Pearson's goodness of fit test $p = 0.40$; Hosmer-Lemeshow goodness of fit test $p = 0.76$; Akaike Information Criterion (AIC) = 85.9). The model predicted survival with an area under the ROC curve = 0.84, compared to that of the PIM I ROC curve = 0.66 (see Figure 4.4).
Figure 4.4: Final model receiver operating characteristic (ROC) curve for survival.

At a probability cut-off ($\pi_0$) for survival of 0.5, the model predicted survival with 87.5% sensitivity; 59.3% specificity; 81.7% positive predictive value; and 69.6% negative predictive value. The proportion correctly classified was 78.3%. The plot of sensitivity and specificity is shown in Figure 4.5.

It can be seen that the probability cut-off threshold $\pi_0$ might be adjusted upward to approximately 0.70, which would allow increased specificity, equal to sensitivity, at approximately 80%. However, increasing the probability cut-off beyond 0.70 would result in a dramatic fall-off in the sensitivity of the model.
Adjusted odds of survival in the multivariate predictive model

Adjusted odds ratios (95% CI) for survival are shown in Table 4.7. After adjusting for the variable weight, increased admission potassium, increased lactate, and increased corrected chloride were all independent predictors of nonsurvival, whereas increased albumin was an independent predictor of survival.

Each 1 mmol/L increase in admission potassium was associated with 34% lower relative odds of survival (95% CI 3 - 55%); each 1 mmol/L increase in lactate with 15% lower relative odds of survival (95% CI 4 - 26%); and each 1 mmol/L increase in corrected chloride with 11% lower relative odds of survival (95% CI 0.1 - 20%). By contrast, each 1 g/L increase in albumin was associated with an 11% higher relative odds of survival (95% CI 2 - 22%). However, the effect of weight on survival could not be distinguished from chance at the 5% significance level.
Table 4.7: Adjusted odds ratios for survival.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>0.90</td>
<td>0.79 – 1.02</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>0.66</td>
<td>0.45 – 0.96</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>1.11</td>
<td>1.02 – 1.22</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.85</td>
<td>0.74 – 0.96</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>0.89</td>
<td>0.80 – 0.99</td>
</tr>
</tbody>
</table>

Checking the predictive model

The plot of standardized residuals (see Figure 4.6) did not reveal significant outliers.

Figure 4.6 Standardized Pearson residual plot
However, the plot of leverage identified 2 influential observations with high leverage (see Figure 4.7) - these were both nonsurvivors, one child with moderately high admission lactate, normal albumin, and a very high potassium (9.7 mmol/L); and one child with a higher than average weight (26 kg).

Figure 4.7: Leverage plot

The child with admission potassium = 9.7 mmol/L was judged to be an extreme outlier, and therefore the model was re-run without this patient, to assess the effect on the model. The effect of excluding this child from the analysis was a slight increase in the relative odds of survival for admission potassium (OR = 0.78; 95% CI 0.50 – 1.14); and corrected chloride (OR 0.90; 95% CI 0.81 – 1.01), neither of which could be distinguished from chance at the 5% significance level. However, since the effect of excluding the outlying observation was not large, in terms of the magnitude and direction of the associations, this observation was retained in the final model.
Multivariate linear regression models: PICU-dependency

Multivariate linear regression models for the following PICU-dependent variables were also developed:

**Day-28 alive-and-ventilator-free days**

\[ = 37.7 - (0.5 \times \text{Lactate}) - (1.6 \times \text{Potassium}) - (0.2 \times \text{cChloride}) + (0.4 \times \text{Albumin}) + (0.1 \times \text{Strong ion gap}) \]

After adjusting for these co-variables, Day-28 alive-and-ventilator-free days decreased on average by 0.5 days (95% CI 1.02 – 0.01) for each 1 mmol/L increase in admission lactate; and by 1.6 days (95% CI 3.00 – 0.23) for each 1 mmol/L increase in potassium. Each 1 g/L increase in albumin was associated with an average increase of 0.4 (95% CI 0.05 – 0.69) Day-28 alive-and-ventilator-free days. However, changes in Day-28 alive-and-ventilator-free days associated with corrected chloride and strong ion gap could not be distinguished from chance at the 5% significance level.

**Day-28 alive-and-inotrope-free days**

\[ = 66.2 - (0.5 \times \text{Weight}) - (0.9 \times \text{Lactate}) - (1.4 \times \text{Potassium}) - (0.3 \times \text{cChloride}) + (0.3 \times \text{Albumin}) \]

After adjusting for co-variables, Day-28 alive-and-inotrope-free days decreased on average by 0.9 days (95% CI 0.4 – 1.4) for each 1 mmol/L increase in admission lactate; and decreased by 1.4 days (95% CI 0.1 – 2.8) for each 1 mmol/L increase in potassium. On average, each 1 g/L increase in albumin was associated with an additional 0.3 Day-28 alive-and-inotrope-free days (95% CI 0.1 – 0.6) for each. However, changes in Day-28 alive-and-inotrope-free days associated with weight and corrected chloride could not be distinguished from chance at the 5% significance level.

**Day-28 alive-and-ICU-free days**

\[ = 29.5 - (0.5 \times \text{Lactate}) - (1.5 \times \text{Potassium}) - (0.1 \times \text{cChloride}) + (0.4 \times \text{Albumin}) + (0.02 \times \text{Strong ion gap}) \]

After adjusting for co-variables, Day-28 alive-and-ICU-free days decreased on average by 0.5 days (95% CI 0.94 – 0.02) for each 1 mmol/L increase in admission lactate.
lactate; and by 1.5 days (95% CI 2.8 – 0.28) for each 1 mmol/L increase in admission potassium. Each 1 g/L increase in albumin was associated with an additional 0.4 Day-28 alive-and-ICU-free days days (95% CI 0.1 – 0.68). However, changes in Day-28 alive-and-ICU-free days associated with admission corrected chloride and strong ion gap could not be distinguished from chance at the 5% significance level.

Discussion

This chapter has described the metabolic acid-base disturbances of a moderately large group of children with septic shock in terms of a modified Fencl-Stewart approach. This group of children was characterized by high predicted and observed mortality, and severe metabolic acidosis, associated with moderate hyperlactataemia and hyperchloreaemia, and severe hypoalbuminaemia.

In more than 80% of cases, the aetiology of metabolic acidosis was mixed, with hyperlactataemia-hyperchloreaemia combinations predominating. It is striking that although mixed metabolic acidoses due partly to hyperlactataemia were common (76%), metabolic acidosis due only to hyperlactataemia was rare. Similarly, it is notable that more than 80% of metabolic acidosis was due to in part to hyperchloreaemia, but metabolic acidosis due to hyperchloreaemia alone occurred in only 11% of cases. Although elevation of the strong ion gap did contribute to metabolic acidosis, particularly in combination with lactate-driven and chloride-driven acidoses, the prevalence of strong ion gap-driven acidosis was much lower.

Partition of the base excess confirmed that the major negative base excess effects were due to (excess) chloride, lactate, and the 'unmeasured' anions contributing to the base excess gap. Note that the base excess gap and the strong ion gap are not interchangeable concepts, since certain of the 'unmeasured' anions (and cations) contributing to the base excess gap are 'measured' for the purposes of the strong ion gap calculation. The major positive base excess effects were due to (lack of) albumin, and it is apparent that the albumin effect contributed to clinically significant masking of the severity of the underlying metabolic acidosis, given that the net total base excess would have been approximately 5 mEq/L lower in the presence of a normal serum albumin.

The median lactate of 4.8 mmol/L is higher than that reported in children with septic shock by Dugas and colleagues (2.5 mmol/L), similar to that reported by the author among children with shock of heterogeneous aetiology (5.1 mmol/L), and higher than
reported by O'Dell among children with meningococcal septic shock (2.5 mmol/L)[35, 49, 93]. The study of 60 children with meningococcal septic shock may serve as the best comparator for benchmarking the severity of acid-base derangements and outcome in this study population[35]. The group of children with septic shock that is described in this study demonstrated more than twice the net base deficit, almost twice the alkalisising effect due to hypoalbuminaemia, and a several-fold higher chloride effect, although the component of the base deficit due to 'unmeasured' anions was similar (-10 mEq/L)[35]. The PICU mortality rate of 33% in this study is higher than that reported for children with meningococcal septic shock in a developed country setting(10%), although the standardised mortality rate (1.1) is more closely comparable[35].

As expected, the crude statistical analysis demonstrated that mortality due to septic shock was associated with higher admission lactate and lower albumin, similar to previous findings by Weil, Bakker, and Day among adults, and by the author in children with shock of heterogeneous aetiology[3, 16, 49, 96]. It is also notable that this effect was independent of the use of epinephrine by infusion. The ROC analysis for mortality prediction demonstrated that the admission lactate and albumin levels were moderately good predictors of PICU mortality, with area under the ROC curves similar to the PIM 1 score[2].

However, there was no difference in strong ion gap between survivors and nonsurvivors, consistent with the study of Cusack, but contrary to the findings of Balasubramanyan, although, as mentioned previously, direct comparison with the last-mentioned study is difficult since lactate was included as an 'unmeasured' anion[40, 52]. Contrary to initial expectation, net base excess was also significantly lower in nonsurvivors, consistent with the findings of Smith and co-workers among adults, but in contrast to previous findings in children with shock and severe sepsis [7, 49, 102]. However, after adjusting for weight and admission potassium in the multivariate model, base excess and standard bicarbonate were not significantly and independently associated with outcome. The admission strong ion gap and standard bicarbonate levels also showed poor discriminatory power for outcome using the area under the ROC curve.

The final multivariate predictive model, adjusted for weight, included admission potassium, lactate, corrected chloride, and albumin. This model explained approximately 29% of variation in survival, which is perhaps better than expected,
given that other (non-acid-base) admission variables, not to mention post-admission PICU treatment, would be expected to have a significant effect on PICU outcome. In particular, this model does not contain any haemodynamic or ventilatory physiological variables, such as heart rate, blood pressure, or measures of oxygenation and ventilation[2]. The PIM 2 score, developed subsequently, and in current use in the ICU since 2005, might have fared better in this patient group than the PIM 1 score compared here[107]. It should also be noted that the model developed here requires external validation in a larger multi-centre study of children with septic shock of diverse etiology.

After adjusting for co-variables such as weight, only increases in admission lactate, potassium, and corrected chloride, were independently associated with decreased relative odds of survival; whereas increases in albumin were independently associated with increased relative odds of PICU survival. In the case of lactate and albumin, these findings confirm the results of previous work in a smaller group of children with shock[49]. However, the finding from the multivariate model that increased corrected chloride is independently and significantly associated with a poor survival outcome contrasts with the previous work of this author in children with shock, and does not support the original hypothesis that hyperchloremia is a benign phenomenon[49]. Since 0.9% saline was not routinely used for intravascular volume resuscitation, this finding cannot be ascribed to administration of fluids with excess chloride load[43, 59]. It is tempting to speculate that hyperchloremia in these children with septic shock may reflect severe, irreversible renal injury, rather than reversible tubular damage, despite the fact that the adverse effect of hyperchloremia appears to be independent of potassium. Therefore, although the findings of this study with respect to hyperchloremia are not in agreement with previous findings in children, or with those of Rocktaeschel, Brill, and Dondorp in adults, the poor outcome observed among those children with high chloride is consistent with the adverse effects of chloride administration on haemodynamics and inflammatory cytokines that have been seen in animal models[11, 53, 54, 60, 61]. The question of whether metabolic acidosis due to isolated hyperchloremia justifies escalation of haemodynamic support (intravascular volume replacement or inotropic support) in the PICU setting remains unanswered. Unfortunately, given the small number of children with septic shock who had such an isolated hyperchloremic metabolic acidosis, this study is unable to answer that question directly. In fact, it may be the case that isolated hyperchloremia is a relatively uncommon
strong ion gap was not independently associated with PICU-dependency, leading to increased concern over children who were not eligible for transfer; however, the PICU-association between progression of PICU support and days alive and free from ventilatory support, non-ICU support, and decreased from increased admission score and mortality, and decreased survival on ICU-free days. Surgeon models of Day-25 ventilator-free, non-ICU free, and ICU-free days outcome were held for the measure of ICU-dependency as measured using the outcome scores held for the measure of ICU-dependency as measured using the associations between the underlying and disease determinants and PICU.

The associations cannot be explained further. However, given the lack of specific renal dysfunction data, the hypothesis of a higher association between higher position and mortality in these children with specific complications in some instances with higher association due to renal failure, which explain the patterns of observed associations. By contrast, elevation of creatinine to non-ICUfree days in survivors with significant mortality may explain the association, which would not be associated with higher position. As in simulation of the "N. A. P. T. E. E. " with pre-renal hypoperfusion due to intravascular contraction with the hypothesis of exogenous or endogenous extracellular-driven association with the observed regression of non-survivors was non-high, and in fact, the relation between higher position and worse outcome was interesting.

The phenomenon in children with severe shock (49) appears that the presence of these "unmeasured" variables (other than age) is a significant of occult brain injury, and poor progress cannot be supported, and a better balance of the evidence presented, the view of increased score was called "severe shock," would be represented in the strong gap (52). However, on colher cellular injury and therefore highly predictive of PICU morality (52), these so-called severe shock, the assumption that measured "unmeasured" scores might be indicative of severe late injury has been not independently associated with outcome in the multifaceted model. It has been noted that determination of the strong gap occurred in more than half of cases with admission determination of the strong gap occurred in more than half of cases with
further credence to a benign view of strong ion gap derangements, at least in the setting of paediatric septic shock.

An important limitation of this work is that pre-ICU administration of lactate-containing intravenous solutions may have contributed to hyperlactataemia in these children. However, since pre-ICU fluid data were not collected the extent to which the observed hyperlactataemia was iatrogenic, as opposed to intrinsic, cannot be determined. It is also possible that pre-ICU administration of larger volumes of lactate-containing solutions to sicker children might confound the association between hyperlactataemia and increased mortality. However, this argument is countered by the observations of Carcillo et al, showing that mortality in septic shock is lower in children given larger volumes of intravenous fluid[1]. Secondly, direct comparison of the mortality outcome data in this study with those of other recent paediatric studies may be limited by the ability to benchmark risk of mortality data[35]. The PIM 1 score was used to predict mortality at the beginning of this study in 2003, and although the PIM 2 score was in routine clinical use in the PICU by 2005, the PIM 1 score was used throughout the study to maintain consistency[2, 107]. A third limitation is that children were eligible for enrolment if they had a clinical diagnosis of septic shock, without a requirement for microbiological confirmation of an aetiological agent[103]. The consequence of these enrolment criteria was that the septic focus or underlying cause of septic shock was unknown in approximately one third of children, and it is acknowledged that some of the children in the study group would not have met stricter diagnostic criteria. However, it is highly relevant that the nature of the study group, i.e. children with a clinical diagnosis of septic shock, reflects precisely the type of patient faced by the clinician at the time of admission to PICU.

Conclusion
These children with septic shock, who had relatively high predicted and observed mortality rates, demonstrated severe acidaemia and metabolic acidosis, characterised by hyperlactataemia, hyperchloraemia, and to a lesser extent, elevation of the strong ion gap.

The majority of metabolic acidoses were of mixed aetiology, with lactate- and chloride-driven metabolic acidosis predominating. Severe hypoalbuminaemia provided a clinically significant positive contribution to the net observed base excess,
with the result that the true magnitude of the metabolic acidosis would be underestimated by the base excess.

In a multivariate logistic regression model, adjusting for weight, the admission lactate, potassium, corrected chloride, and albumin levels were independent predictors of PICU survival in children with septic shock, with good predictive power. This model requires external validation in a larger multi-centre study of children with septic shock of diverse aetiology.

Elevated lactate and potassium, decreased albumin, and, contrary to the original hypothesis, increased corrected chloride, were associated with lower relative odds of survival. Elevated strong ion gap was not independently associated with either PICU outcome, or PICU dependency, a finding that supports a benign view of this acid-base disturbance.
Chapter 5
Lactate and the lactate:pyruvate ratio in children with septic shock

Introduction:
In the previous chapter, it was demonstrated that the admission lactate level was highly predictive of mortality in children with septic shock, even after adjusting for potentially confounding co-variables in a multivariate model. The questions that follow from this finding are: What are the mechanisms leading to lactate accumulation in septic shock, and can these mechanisms be differentiated on the basis of measured parameters, in order to improve the predictive power of the prognostic model?

Mechanisms of lactate accumulation
Under normal physiological conditions, most ATP is generated by metabolism of glucose via oxidative phosphorylation, with cytoplasmic conversion of glucose to pyruvate, followed by conversion of pyruvate to acetyl CoA by the enzyme pyruvate dehydrogenase, and ultimately followed by mitochondrial oxidation[13, 14]. However, when oxidative phosphorylation is limited by cellular hypoxia, ATP is supplemented by anaerobic glycolysis, and a relatively small amount of ATP is formed, in conjunction with lactate[13, 14]. Lactate production is further accelerated by build up of reduced nicotinamide adenine dinucleotide (NAD), which shifts the reversible lactate dehydrogenase reaction in favour of conversion of pyruvate to lactate[3, 14].

The effect of this shift is a relative excess of cytosolic lactate compared to pyruvate, with elevation of the lactate:pyruvate ratio under conditions of hypoxia. These effects have been demonstrated experimentally in human subjects breathing hypoxic gas mixtures[109]. Huckabee showed in 1958 that although lactate accumulated in humans breathing 13% oxygen mix, this was accompanied by a parallel increase in pyruvate. However, when a 10% oxygen mix was used, there was an increasing discrepancy between excess lactate and the level of pyruvate[109].

This model of lactate accumulation may well be applicable to situations of global body hypoxia-ischaemia, such as after resuscitation from cardiorespiratory arrest, or severe cardiogenic, or haemorrhagic shock. In 1970, Weil and Afifi showed in a rat model that, during experimental haemorrhage, cumulative oxygen debt correlated with excess lactate, and that both oxygen debt and lactate predicted mortality[3].
However, Huckabee and Weil pointed out some of the pitfalls of using lactate and pyruvate as a surrogate for organ hypoxia. Weil showed that the time of sampling is critical for interpretation of these parameters, since pyruvate rose earlier and at a faster rate than lactate, before reaching a plateau, with the result that the lactate:pyruvate ratio only rose substantially after approximately 2 hours of controlled haemorrhage[3]. Second, Huckabee noted that observed changes in arterial lactate and pyruvate provide no information about the state of oxygenation of functional subdivisions or organ systems, indicating only the net result of those organ system effects[109]. For example, it is possible that, at any given time, lactate may be produced by ischaemic gut and simultaneously cleared by skeletal muscle, with both processes being confounded by differential rates of release of lactate and pyruvate into the systemic circulation[109]. Nevertheless, it is this mechanism, hypoxia-driven lactate accumulation, which has classically been put forward to account for the observed associations between raised lactate, multi-organ failure, and mortality in critical illness, and spurred attempts to link lactate accumulation, global oxygen supply-demand variables, and outcome in sepsis[3, 16, 94, 95].

**Lactate accumulation and hypoxia-ischaemia in sepsis**

When mitochondrial oxygen delivery fails, the rate of mitochondrial pyruvate utilisation also falls, and since glycolysis and pyruvate production are ongoing, with the reversible lactate dehydrogenase reaction shifted in favour of lactate, lactate accumulates with an increased lactate:pyruvate ratio[14]. However, several factors suggest that the global hypoxia-ischaemia paradigm is not sufficient to explain lactate accumulation in sepsis, nor does it adequately explain the association with poor outcome in this setting[110-112]. Firstly, Ronco showed that the critical threshold for oxygen delivery is lower than that previously reported in humans, and that sepsis does not alter the critical oxygen delivery level for anaerobic metabolism[112]. Secondly, Hotchkiss demonstrated in a septic rat model that there is no evidence of bio-energetic failure in muscle, liver, heart, and brain, using in vivo phosphorus 31 nuclear magnetic resonance spectroscopy, [18F]fluoromisonidazole, and microfluorometric enzymatic techniques[111]. Lastly, Gore et al used dichloroacetate (DCA), a compound that increases pyruvate oxidation by stimulation of pyruvate dehydrogenase in the presence of sufficient mitochondrial oxygen supply, to assess the role of hypoxia in lactate production in patients with septic shock and healthy volunteers[110]. In that study, although oxygen consumption, rates of glucose and pyruvate production, and pyruvate oxidation were greater in septic patients, administration of DCA resulted in a further increase in oxygen consumption,
decreased glucose, and decreased pyruvate production, with a corresponding decrease in lactate[110]. The authors interpreted these findings as indicating that accumulation of lactate during sepsis is not the result of limitation of mitochondrial oxygen supply. Taken together, these studies suggest that the increase in lactate production seen in patients with sepsis is not necessarily due to cellular hypoxia[110-112]. These findings are also consistent with findings of clinical studies that demonstrated de-linking of the prognostic value of lactate from that of oxygen delivery and consumption variables[16, 94, 95].

Other mechanisms of lactate accumulation in sepsis

It can be seen from the evidence presented so far that the mechanism of lactic acidosis in septic shock cannot be explained according to the traditional type A clinical classification, but it is also becoming clear that the catch-all type B non-hypoxic lactic acidosis is too blunt an instrument for understanding of lactate accumulation in sepsis[14, 15]. Several potentially overlapping mechanisms have been proposed, although differentiation is complicated by differential rates of production and clearance, an effect that is amplified in sepsis by disturbances in microvascular control and microthrombosis that result in marked perfusion heterogeneity, even within the same organ system[3, 14, 109]. Most of the suggested mechanisms hinge on altered regulation of glycolysis in sepsis, including enhancement of phosphofructokinase with increased glycolytic flux, and inactivation of pyruvate dehydrogenase (PDH), the enzyme that controls the unidirectional conversion of pyruvate into acetyl-coA[14]. Whereas, normally, entry of pyruvate into the Krebs cycle is accelerated by depletion of mitochondrial ATP, inhibition of PDH in sepsis would result in cytosolic pyruvate accumulation and an increase in lactate by a mass effect, with a normal lactate:pyruvate ratio[14]. However, the work of Gore et al showing a higher rate of pyruvate oxidation in septic patients contradicts the hypothesis that lactate accumulation in sepsis is due to impairment of pyruvate dehydrogenase activity and limited entry of pyruvate into the Krebs cycle[110].

In the last decade it has become increasingly accepted that although lactate may be produced by hypoxic tissues in sepsis and septic shock, lactate is also produced by fully oxygenated tissues[113]. Gallet and colleagues reported an adult case of septic shock in which, although the lactate level and lactate:pyruvate ratio remained persistently elevated, therapeutic increases in systemic oxygen delivery failed to increase oxygen consumption[88]. Those findings suggest that although occult hypoxia was suspected at the tissue or organ level, oxygen supply dependency did
not exist at the net global or systemic level[88]. Therefore, the observed systemic changes in arterial lactate will be a determined by the net balance between increases in production and decreases in clearance, across all organ systems[113]. There may be net production of lactate in skeletal muscle, ischaemic gut, and acutely injured lungs, but net clearance of lactate by liver glycogenolysis, and utilisation of lactate as an energy substrate by the heart and brain[113].

Debate has focused on whether the hyperlactataemia of sepsis is predominantly a function of increased lactate production, or decreased lactate clearance[113]. Recently, several elegant studies have attempted to answer this question[20, 21, 114]. Lavraut and colleagues modeled lactate kinetics in adults with sepsis, using a controlled infusion of L-lactate, and classified patients according to their baseline lactate into either hyperlactataemic (mean lactate 2.6 mmol/L) or normal lactate groups[114]. Hyperlactataemic patients showed lower lactate clearance than those with normal lactate, although their rates of lactate production were similar, suggesting that this mild hyperlactataemia in sepsis was due to defective lactate utilisation[114]. Revelly and co-workers evaluated lactate production and clearance in adult patients with septic shock (mean lactate 3.2 mmol/L), as well as in patients with cardiogenic shock and normal volunteers, using controlled infusions of labeled glucose and sodium lactate[21]. However, in contrast to the findings of Lavraut et al, lactate clearance was similar in sepsis, cardiogenic shock, and controls, whereas endogenous lactate and endogenous glucose production were higher in patients with both septic and cardiogenic shock, compared to controls. Those findings suggest that the predominant mechanism of lactate accumulation in both these shock states is accelerated glycolysis, which exceeds the oxidative capacity of the mitochondria to remove pyruvate[21].

Other investigators have addressed the issue of whether aerobic glycolysis might be up-regulated in sepsis through stimulation of the skeletal muscle Na⁺ K⁺ ATPase, by circulating or exogenous epinephrine[24, 115]. Since skeletal muscle represents approximately 40% of tissue body mass, this mechanism would be quantitatively very important. Luchette et al manipulated the Na⁺ K⁺ pump with ouabain during epinephrine infusion and controlled haemorrhage in a rat model, while measuring local lactate levels with a microdialysis probe[115]. Lactate levels rose during both epinephrine infusion and controlled haemorrhage, but inhibition of the Na⁺ K⁺ pump with ouabain resulted in a fall in lactate[115]. Levy and colleagues used microdialysis techniques in adults with septic shock (mean lactate 4.0 mmol/L) to show that
selective inhibition of skeletal muscle Na\(^+\) K\(^+\) ATPase by ouabain infusion halted overproduction of lactate and pyruvate\[24\]. These findings indicate that although hyperlactataemia may be associated with adverse outcome, this association is not based upon the mechanism of tissue hypoxia-ischaemia, but rather due to acceleration of aerobic glycolysis by stimulation of the skeletal muscle Na\(^+\) K\(^+\) ATPase\[16, 87, 94-100\].

The implications of these findings for clinical studies are that lactate accumulation, due primarily to accelerated aerobic glycolysis or decreased lactate clearance might be inferred from a normal lactate:pyruvate ratio, whereas elevated lactate due mainly to tissue hypoxia-ischaemia might be detected on the basis of an elevated lactate:pyruvate ratio. It follows that, since lactate levels do have important prognostic significance in septic shock among children and adults, it would be important to determine whether the association between elevated lactate and poor outcome might differ, according to whether tissue hypoxia or accelerated glycolysis was suggested by the lactate:pyruvate ratio\[16, 87, 94-100\]. It remains to be seen whether the association between elevated lactate and mortality is a function of circulating epinephrine, glucose accumulation, or independent of the underlying mechanism of raised lactate. In fact, the hypothesis that lactate might not be a universally adverse metabolite is supported by the observation that lactate may function as an important substrate fuel for the myocardium in shock states\[116\].

The lactate:pyruvate ratio and outcome in sepsis

The work of Weil and Affi in 1970, among 142 adults with ‘circulatory shock’, demonstrated that nonsurvivors (56%) could be differentiated from survivors on the basis of the admission lactate level\[3\]. However, it is possible that further studies of the prognostic value of the lactate:pyruvate ratio in septic shock might have been discouraged by their finding that the calculation of the lactate:pyruvate ratio did not add to the prognostic value of lactate alone\[3\]. Yet, it is notable that only 10% of their patients suffered from septic shock, and we might have expected that the underlying conditions, such as cardiogenic and hypovolaemic shock, were more closely analogous to the classical model of hyperlactataemia and hypoxia-ischaemia than is the case in sepsis. Furthermore, although mean lactate was 2.3 mmol/L in survivors compared to 12.4 mmol/L in nonsurvivors, the lactate:pyruvate ratio was only 17.5 in survivors compared to 36.9 in nonsurvivors, suggesting that the lactate:pyruvate ratio was still a potentially useful prognosticator in this patient group\[3\].
More recently, a handful of studies have evaluated the prognostic value of the lactate:pyruvate ratio in sepsis, including one pilot study in children[87, 93, 96]. The study of Levy and co-workers of 60 adult patients with septic shock requiring vasopressor therapy, showed that those who died during the first 24 hours had a higher mean admission lactate (12.2 mmol/L) than those who died after 24 hours (4.6 mmol/L), but also that those patients who died early showed a higher lactate:pyruvate ratio (mean 37) compared to later nonsurvivors (mean 20)[87]. By contrast, the lactate:pyruvate ratio was of little benefit in distinguishing ICU survivors (mean 19) from ICU nonsurvivors (mean 20) overall, with an elevated lactate:pyruvate ratio having 77% sensitivity and 68% specificity for prediction of outcome [87]. In this regard, both the lactate level and the pyruvate level were elevated in survivors and nonsurvivors[87]. These authors also included a small comparison group of patients with cardiogenic shock, in whom the lactate:pyruvate ratio was significantly higher than among patients with septic shock, suggesting that oxygen supply dependency did indeed exist among patients with cardiogenic shock[87].

In the study by Day and colleagues of 346 adults with severe malaria, hyperlactataemia was strongly associated with mortality (relative risk 4.3), but so was the lactate:pyruvate ratio (median 30 in survivors, compared to 63 in nonsurvivors)[98]. However, after adjusting for confounding factors such as renal failure and liver dysfunction, only the base deficit, not the admission lactate or the lactate:pyruvate ratio, was independently predictive of mortality[98]. Finally, Dugas et al also examined the course of oxygen delivery variables, bicarbonate, lactate, and the lactate:pyruvate ratio, in a pilot study of 11 children with septic shock[93]. Since the patient group was very small and there were no nonsurvivors, only limited conclusions could be drawn, although downward trends in bicarbonate and lactate were noted during recovery. However, the authors commented on at least one patient in whom the lactate:pyruvate ratio was persistently elevated, but with a normal lactate level, suggesting increased pyruvate utilisation, rather than lactate accumulation due to tissue hypoxia[93].

Aims
The aims of this study were, first, to measure the frequency and severity of elevation of the lactate:pyruvate ratio in children with septic shock; second, to describe the clinical and biochemical features associated with elevation of the lactate:pyruvate ratio in these children; third, to describe the relationship between metabolic acidosis,
Inotropic support, as described in the previous chapter, therapy, lactate-contraining
Routine management of septic shock, including use of intravenous fluids and
Routine management of septic shock

Inotropic support and were not prescribed on the basis of derangements or severity of illness.
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University research ethics committee. Eighty children were enrolled with the
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Subsequent laboratory confirmation of microbiological infection was not required in order
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Hypoxemia, or oxygen plus hyperventilation of hyperventilation, hypercarbia, tachypnoea.
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Interosseous volume depredation in the presence of acute encephalopathy.
Interosseous volume depredation in the presence of acute encephalopathy.

seconds), which were responsive to inotropic induction or fluid resuscitation or
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pressure of higher inotroponation for age, or profound ventricular failure (time > 5
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were eligible for enrollment. A clinical diagnosis of septic shock was made in the
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support (due to fluid therapy or inotropic support) at the time of admission to PICU
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All children with a clinical diagnosis of septic shock who required hemodynamic
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usually 30–60 minutes of intravenous fluid boluses, was unsuccessful.
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Department resuscitation to correct a persistent interosseous volume depredation.
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Children with septic shock would usually only be referred to PICU if immediate emergency
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paramedic transfer after stabilization from local, district, and other regional centers.
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Chapter 4: Therapy. Children with septic shock are admitted to the PICU directly from
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The characteristics of the patients with septic shock are described in more detail in
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Pediatric
Pediatric

previous chapter.
previous chapter.

2002. The structure, staffing, and patient profile of the PICU are described in detail in
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Children's Hospital, Cape Town, over the 2-year period from February 2003 to March
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The study was performed in the pediatric intensive care unit of Red Cross
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Setting
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Materials and methods
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Dependent and outcome using a multivariate model
Dependent and outcome using a multivariate model

The association between elevation of the lactate/pyruvate ratio, measure of ICU
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hypoperfusion, and development of the lactate/pyruvate ratio, and ease of describe
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solutions, such as Ringer's lactate, were the resuscitation fluids of choice for repletion of intravascular volume, both before and during PICU admission. Normal (0.9%) saline was rarely used for treatment of septic shock. Administration of sodium bicarbonate for correction of metabolic acidosis, whether due to hyperchloremia or hyperlactateemia, was not recommended PICU practice at the time of the study. Dopamine or dobutamine were the first line inotropic agents of choice. Epinephrine or norepinephrine might be added for refractory hypotension despite adequate fluid therapy. PICU management might also include the use of alternative inotropic agents, such as the phosphodiesterase inhibitor milrinone, but all these changes would usually be made after admission blood sampling.

**Blood sampling and data collection**

On admission to PICU, a single sample of arterial blood was immediately obtained from the indwelling cannula for arterial blood gas analysis, measurement of routine electrolytes, lactate, and pyruvate. Arterial pH, pCO2, standard bicarbonate, standard base excess (BE), and lactate, were measured and derived using a Radiometer ABL 520 blood gas analyser (Copenhagen, Denmark). Serum electrolytes were measured by the ion-specific electrode method using a Beckman CX9 Pro analyser (Berlin, Germany). Serum albumin was measured by the reagent method using a Beckman CX9 Pro analyser (Berlin, Germany). Strong ion difference and strong ion gap (SIG) were calculated from the laboratory electrolyte and acid-base data, using the standard formulae, as previously described[32, 34, 49].

One mL of the same arterial blood specimen was immediately placed in a perchloric acid medium, placed in a freezer and stored at -80 degrees Celsius. Pyruvate samples were subsequently analysed in batches using high performance liquid chromatography (HPLC) with fluorescein detection, with a coefficient of variation of less than 15% (Ampath Laboratories, Pretoria, South Africa).

Metabolic acidosis was defined as standard bicarbonate < 22 mmol/L and thresholds for clinically significant biochemical derangements were defined *a priori* as lactate > 2 mmol/L, pyruvate > 0.1 mmol/L, and lactate:pyruvate ratio > 20[49, 90, 105, 108]. Aetiology of metabolic acidosis was assigned to hyperlactataemia (lactate > 2mmol/L), hyperchloremia (corrected chloride > 110 mmol/L), strong ion gap (SIG > 2 mmol/L), or in the case of mixed acidosis, any combination thereof (see previous chapters).
Clinical diagnoses, underlying or pre-existing conditions, predicted risk of mortality (Paediatric Index of Mortality 1 during the study period), duration of mechanical ventilation, duration of inotropic support, and duration of PICU stay (expressed as calendar days, or part thereof), and observed PICU mortality, were recorded and Day-28 'alive and ventilator-free', ‘alive and inotrope-free', and 'alive and ICU-free' days, were calculated[2].

Statistical considerations
Data are reported as median (interquartile range; IQR) (range); n (%); and 95% confidence intervals (95% CI). In the crude analysis, non-parametric continuous data were analysed by the Mann-Whitney and Kruskal-Wallis tests, and categorical data by the Fisher's Exact test or the Chi-squared test for trend as appropriate, using Analyse-It statistical software (Analyse-It, UK).

In the bivariate analysis, linear regression was performed using the explanatory variables epinephrine infusion, age, weight, lactate, and pyruvate were entered, with lactate:pyruvate ratio as the outcome variable. Logistic regression was performed using the categorical outcome variable survival, and the explanatory variables, age, weight, epinephrine infusion, standard bicarbonate, lactate, pyruvate, albumin, strong ion gap, and lactate:pyruvate ratio.

In the multivariate analysis, a forward (non-automated) logistic regression model was developed, using the outcome variable survival and explanatory variables selected on the basis of clinical interest and significance of the association in the preceding bivariate analysis. Bivariate and multivariate regression analyses were performed using Intercooled Stata version 8.2 statistical software (Statacorp, Texas, USA).

Results
Eighty-three children with a clinical diagnosis of septic shock were enrolled, of whom 5 children (6%) were diagnosed with meningococcal disease. Median age was 4.8 months (IQR 4.4 - 8.5) and median weight 6.5 kg (IQR 4.5 - 8.0). Seventy-six children (92%) were mechanically ventilated and 10 children (12%) were receiving epinephrine, at the time of admission to PICU. Median predicted mortality (PIM 1) was 0.30 (IQR 0.12 - 0.50). There were 27 nonsurvivors (observed mortality 33%) and 56 survivors (67%).

Complete acid-base, biochemical, and ICU dependency data, are given in Chapter 4.
The relevant admission biochemical data, including lactate, pyruvate, and lactate:pyruvate ratios, are summarised in Table 5.1.

Table 5.1:
Selected admission biochemical and acid-base data (n = 83).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.19</td>
<td>7.03 - 7.36</td>
</tr>
<tr>
<td>Standard bicarbonate (mmol/L)</td>
<td>11.9</td>
<td>9.0 - 16.1</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>4.8</td>
<td>2.1 - 10.3</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.19</td>
<td>0.03 - 0.59</td>
</tr>
<tr>
<td>Lactate:pyruvate ratio</td>
<td>25.3</td>
<td>5.8 - 115.8</td>
</tr>
<tr>
<td>Corrected Chloride (mmol/L)</td>
<td>115</td>
<td>111 - 120</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>20</td>
<td>15 - 26</td>
</tr>
<tr>
<td>Strong ion gap (mEq/L)</td>
<td>3.1</td>
<td>0.7 to 6.1</td>
</tr>
</tbody>
</table>

This group of children with septic shock was characterised by moderate-severe acidaemia (median pH 7.19), hyperlactataemia (median lactate 4.8 mmol/L), hyperchloreaemia (median corrected chloride 115 mmol/L), and hypoalbuminaemia (median albumin 20 g/L). In addition, these children demonstrated an elevated lactate:pyruvate ratio (median 25.3), with 55 of the 83 children (66%) having a lactate:pyruvate ratio greater than 20.

Metabolic acidosis and lactate

Seventy-nine children (95%) demonstrated a metabolic acidosis on admission to PICU, which was mixed in 85 children (82%), with hyperlactataemia-hyperchloreaemia-strong ion gap acidosis occurring most commonly (38%), followed by hyperlactataemia-hyperchloreaemia (23%). Hyperlactataemia was the single primary cause of the metabolic acidosis in only 3 children (4%). Overall, hyperchloreaemia (62%) and hyperlactataemia (76%) were the most frequent individual underlying causes of metabolic acidosis. Demographic variables, admission acid-base parameters, and duration of intensive care support for children with metabolic acidosis plus raised lactate; raised lactate only; metabolic acidosis only; and normal lactate without metabolic acidosis, are shown in Table 5.2.
Table 5.2: Children with metabolic acidosis plus raised lactate (↑ Lactate ↓ SB); raised lactate only (↑ Lactate Only); metabolic acidosis only (↓ SB Only); and normal lactate without metabolic acidosis (N lactate N/↑ SB). Data are median (IQR) and n (%).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>↑ Lactate ↓ SB (n=60)</th>
<th>↑ Lactate Only (n=3)</th>
<th>↓ SB Only (n=19)</th>
<th>N lactate N/↑ SB (n=1)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>6.2 (3.8 - 9.5)</td>
<td>7.5 (6.4 - 12.3)</td>
<td>7.0 (5.4 - 8.0)</td>
<td>9.0</td>
<td>0.61</td>
</tr>
<tr>
<td>Predicted mortality (PIM)</td>
<td>0.32 (0.18 - 0.37)</td>
<td>0.11 (0.01 - 0.16)</td>
<td>0.15 (0.08 - 0.42)</td>
<td>0.30</td>
<td>0.03*</td>
</tr>
<tr>
<td>pH</td>
<td>7.19 (7.06 - 7.36)</td>
<td>7.51 (7.44 - 7.57)</td>
<td>7.09 (6.98 - 7.29)</td>
<td>7.29</td>
<td>0.03*</td>
</tr>
<tr>
<td>Standard bicarbonate (mmol/L)</td>
<td>12 (9.0 - 15.9)</td>
<td>25.1 (22.2 - 27.0)</td>
<td>11.4 (8.4 - 15.0)</td>
<td>22.5</td>
<td>NA</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>7.1 (4.2 - 11.4)</td>
<td>4.5 (2.7 - 5.2)</td>
<td>1.3 (1.1 - 1.8)</td>
<td>0.7</td>
<td>NA</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.27 (0.17 - 0.31)</td>
<td>0.17 (0.14 - 0.29)</td>
<td>0.09 (0.06 - 0.11)</td>
<td>0.12</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Lactate:pyruvate ratio</td>
<td>29.0 (22.2 - 38.9)</td>
<td>15.9 (15.5 - 37.1)</td>
<td>15.0 (12.2 - 18.2)</td>
<td>5.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>137 (132 - 144)</td>
<td>130 (129 - 134)</td>
<td>136 (130 - 147)</td>
<td>133</td>
<td>0.34</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 (2.9 - 6.3)</td>
<td>4.2 (3.3 - 5.7)</td>
<td>2.3 (1.6 - 3.7)</td>
<td>3.1</td>
<td>0.009*</td>
</tr>
<tr>
<td>Corrected chloride (mmol/L)</td>
<td>115 (112 - 119)</td>
<td>106 (101 - 108)</td>
<td>120 (119 - 126)</td>
<td>110</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>18 (15 - 25)</td>
<td>18 (15 - 26)</td>
<td>25 (22 - 28)</td>
<td>11</td>
<td>0.02*</td>
</tr>
<tr>
<td>Strong ion gap (mEq/L)</td>
<td>3.1 (1.6 - 6.0)</td>
<td>5.0 (-0.5 to 6.0)</td>
<td>2.9 (-0.6 to 8.9)</td>
<td>5.4</td>
<td>0.85</td>
</tr>
<tr>
<td>D28 ventilator-free days</td>
<td>21 (0 - 25)</td>
<td>26 (0 - 28)</td>
<td>24 (19 - 26)</td>
<td>24</td>
<td>0.11</td>
</tr>
<tr>
<td>D28 inotrope-free days</td>
<td>24 (90 - 26)</td>
<td>28 (8 - 28)</td>
<td>26 (25 - 28)</td>
<td>25</td>
<td>0.01*</td>
</tr>
<tr>
<td>D28 ICU-free</td>
<td>19 (0 - 23)</td>
<td>24 (0 - 24)</td>
<td>23 (18 - 25)</td>
<td>23</td>
<td>0.04*</td>
</tr>
<tr>
<td>Epinephrine infusion</td>
<td>8 (13%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>1 (na)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Survival</td>
<td>35 (58%)</td>
<td>2 (67%)</td>
<td>18 (95%)</td>
<td>1 (na)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

* indicates statistical significance.
In the crude analysis, admission pyruvate; lactate:pyruvate ratio; potassium; corrected chloride; albumin levels; Day-28 inotrope-free and ICU-free days; and the proportion of survivors, all differed significantly across these groups (all p < 0.05). The principal differences were noted between the group with metabolic acidosis plus raised lactate, and the group with metabolic acidosis only. Children with metabolic acidosis plus raised lactate demonstrated a higher pyruvate and higher lactate:pyruvate ratio; higher potassium; lower corrected chloride; and lower albumin, than those children with metabolic acidosis alone. Children with metabolic acidosis plus raised lactate were also more likely to be receiving epinephrine by infusion, and they had fewer inotrope-free and ICU-free days, as well as a lower proportion of survivors, compared to children with metabolic acidosis alone.

**Lactate:pyruvate ratio**

Demographic variables, acid-base parameters, and duration of intensive care support for children with normal (≤ 20) and increased (> 20) lactate:pyruvate ratio are shown in Table 5.3.
Table 5.3: Demographic variables, acid-base parameters, and duration of intensive care support for children with normal (≤ 20) and increased (> 20) lactate:pyruvate (LP) ratio. Data are median (IQR) and n(%). *Denotes statistical significance at the 8% level.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal LP ratio (≤ 20) (n = 65)</th>
<th>High LP ratio (&gt; 20) (n = 28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>7.9 (6.7 - 10.3)</td>
<td>5.4 (3.7 - 8.4)</td>
<td>0.0007*</td>
</tr>
<tr>
<td>Predicted mortality (PIM)</td>
<td>0.28 (0.11 - 0.53)</td>
<td>0.30 (0.18 - 0.50)</td>
<td>0.38</td>
</tr>
<tr>
<td>pH</td>
<td>7.27 (7.09 - 7.39)</td>
<td>7.16 (7.02 - 7.33)</td>
<td>0.08</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>3.7 (3.1 - 5.2)</td>
<td>3.9 (2.9 - 5.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Base excess (mEq/L)</td>
<td>- 11.7 (- 18.1 to - 8.0)</td>
<td>-16.6 (- 21.0 to - 10.9)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Standard bicarbonate (mmol/L)</td>
<td>13.8 (9.9 - 17.8)</td>
<td>11.4 (8.6 - 15.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>4.8 (2.1 - 10.4)</td>
<td>7.2 (4.3 - 11.4)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Pyruvate (mmol/L)</td>
<td>0.19 (0.10 - 0.29)</td>
<td>0.23 (0.13 - 0.290)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Lactate:pyruvate ratio</td>
<td>25.3 (18.0 - 36.2)</td>
<td>30.7 (25.3 - 41.1)</td>
<td>na</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>136 (131 - 144)</td>
<td>116 (111 - 122)</td>
<td>0.93</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.8 (2.2 - 5.1)</td>
<td>4.5 (2.7 - 5.4)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>111 (107 - 122)</td>
<td>111 (107 - 120)</td>
<td>0.61</td>
</tr>
<tr>
<td>Corrected chloride (mmol/L)</td>
<td>116 (111 - 120)</td>
<td>115 (111 - 120)</td>
<td>0.40</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>20 (15 - 28)</td>
<td>17 (15 - 25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Strong ion gap (mEq/L)</td>
<td>3.1 (0.7 - 6.1)</td>
<td>3.1 (1.4 - 6.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>D28 ventilator-free days</td>
<td>23.0 (0 - 25)</td>
<td>22.0 (0 - 25)</td>
<td>0.53</td>
</tr>
<tr>
<td>D28 inotropic-days</td>
<td>25.0 (0 - 27)</td>
<td>23.5 (0 - 27)</td>
<td>0.07</td>
</tr>
<tr>
<td>D28 ICU-free days</td>
<td>20.0 (0 - 24)</td>
<td>19.5 (0 - 23)</td>
<td>0.18</td>
</tr>
<tr>
<td>Epinephrine infusion</td>
<td>3 (11%)</td>
<td>7 (13%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Survival</td>
<td>22 (82%)</td>
<td>33 (59%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
In the crude analysis, it can be seen that children with an increased lactate:pyruvate ratio on admission to PICU had lower body weight; lower base excess; higher lactate; higher pyruvate; and higher potassium, (all $p < 0.05$), as well as a trend towards lower albumin that did not quite reach statistical significance. Strong ion gap did not differ significantly between the two groups.

Children with increased lactate:pyruvate ratio also tended to have fewer inotrope-free days and a lower proportion of survivors, although these differences were not quite significant at the 5% level. Elevated lactate:pyruvate ratio was not associated with use of epinephrine infusion, and the number of Day-28 ventilator-free and ICU-free days did not differ between the two groups.

**Metabolic acidosis, lactate, and lactate:pyruvate ratio**

The frequency of raised lactate:pyruvate ratio among children with and without metabolic acidosis and hyperlactataemia is shown in Figure 5.1.

It can be seen that the 3 most common combinations of lactate-pyruvate acid-base status among children with septic shock are (in descending order of frequency):

- Metabolic acidosis + hyperlactataemia + raised LP ratio (61%)
- Metabolic acidosis + normal lactate + normal LP ratio (19%)
- Metabolic acidosis + hyperlactataemia + normal LP ratio (11%)

Other possible combinations of lactate acid-base status occurred in only 8% of children.
Figure 5.1: Frequencies of metabolic acidosis, hyperlactatemia, and raised LP ratio (LPR) in children with septic shock. Data are n (%) and 95% confidence intervals (CI) for the proportion.
Figure 6.2: Lactate and pyruvate levels in 55 children with raised lactate:pyruvate ratio (LPR).
Data are n (%) and 95% confidence intervals (CI)

- **Raised LPR** (n = 55)
  - 66% (CI 55 - 78%)
  - Hyperlactataemia (n = 52)
    - 63% (CI 51 - 73%)
    - Raised Pyruvate (n = 32)
      - 39% (CI 28 - 50%)
    - Normal/Low Pyruvate (n = 20)
      - 24% (CI 15 - 35%)
  - No Hyperlactataemia (n = 3)
    - 3% (CI 1 - 10%)
    - Raised Pyruvate (n = 0)
      - 0% (CI 0 - 4%)
    - Normal/Low Pyruvate (n = 3)
      - 3% (CI 1 - 10%)
Linear regression model: lactate:pyruvate ratio

A multivariate linear regression model was developed to measure the independent associations between the risk factors epinephrine infusion, age, weight, lactate, pyruvate, and the outcome variable lactate:pyruvate ratio.

The use of epinephrine, age, and weight were not significantly associated with changes in the lactate:pyruvate ratio. These variables also did not alter the effect of co-variables on lactate:pyruvate ratio, and were therefore excluded from the model. In the final model, lactate:pyruvate ratio increased on average by 4.4 (95% CI 4.0 – 4.8) for every 1 mmol/L increase in admission lactate; and fell by 1.1 (95% CI 1.0 – 1.2) for every 0.01 mmol/L increase in pyruvate. This model explained 86% of the variation in lactate:pyruvate ratio (p = 0.00001).

Lactate:pyruvate ratio and survival

In the crude analysis, a raised lactate:pyruvate ratio occurred in 59% of survivors (n = 33 / 56), compared to 82% of nonsurvivors (n = 22 / 27) (p = 0.07). In the bivariate analysis, the unadjusted odds of survival fell on average by 3.7% (95% CI 0.8 – 6.4) for each 1 unit increase in the lactate:pyruvate ratio (p = 0.012, Wald test). Similarly, the relative odds of survival were on average 67% lower (95% CI 1 – 89) among children with a high lactate:pyruvate ratio (> 20) compared to those with a normal lactate:pyruvate ratio (p = 0.036).

Hyperlactataemia with and without elevated lactate:pyruvate ratio

In the crude analysis, a sub-group comparison among all those children with raised lactate (n = 63), showed that the 52 children who also had a raised lactate:pyruvate ratio had a similar proportion of survivors (n = 30; 58%), compared to the 11 children without raised lactate:pyruvate ratio (n = 7; 64%), (p = 0.99).

Multivariate logistic regression model: lactate:pyruvate ratio and survival

When lactate:pyruvate ratio was included as an additional variable in the multivariate predictive outcome model that was described in the Chapter 4 (the model including the explanatory variables lactate, potassium, corrected chloride, and albumin) the lactate:pyruvate ratio was not significantly associated with outcome. Adjusted odds ratio for survival was 1.0 (95% CI 0.98 – 1.05) for each 1 unit increase in lactate:pyruvate ratio (p = 0.99, Wald test).
Since the fit of the predictive model, as measured by Akaike's Information Criterion (AIC) was not further improved with the inclusion of lactate:pyruvate ratio (original model AIC = 87), either as a continuous variable (AIC = 89); as a binary (normal/high) variable (AIC = 89); or with substitution of lactate:pyruvate ratio for the lactate variable (AIC = 88), the lactate:pyruvate ratio was not included as an additional variable in the final model for prediction of outcome in septic shock.

Linear regression models: lactate:pyruvate ratio and ICU dependency

When lactate:pyruvate ratio was included in the predictive model for the number of Day-28 ventilator-free days that had been developed in the previous chapter, it was not independently associated with changes in ventilator-free days after adjusting for the co-variables lactate, potassium, corrected chloride, albumin, and SIG (p = 0.8; Wald test), and therefore it was excluded from the final predictive model.

Similarly, lactate:pyruvate ratio was not independently associated with changes in either Day-28 inotrope-free days or Day-28 ICU-free days, after adjusting for the co-variables in the respective linear regression models.

Discussion

This chapter describes a relatively large group of children with septic shock, characterised by multiple acid-base and biochemical disturbances, including moderate-severe metabolic acidemia, hyperchloremia, hypalbuminemia, hyperlactataemia and elevation of the lactate:pyruvate ratio. In the context of the aetiology of the metabolic acidosis, although raised lactate was an uncommon primary cause, hyperlactataemia was an underlying cause of metabolic acidosis in 76% of cases and more than half of these children demonstrated an abnormally elevated lactate:pyruvate ratio.

Children with metabolic acidosis plus raised lactate had fewer inotrope-free and ICU-free days, and demonstrated greater need for prolonged ICU support, as well as a lower proportion of survivors, compared to children with metabolic acidosis alone. These findings are consistent with the hypothesis that it is lactate, rather than simply metabolic acidosis, that is associated with prolongation of ICU-dependency and mortality[49]. However, it is not yet known whether hyperlactataemia due to hypoxia-ischaemia, signified by an elevated lactate:pyruvate ratio, or hyperlactataemia due to aerobic glycolysis, signified by a normal lactate:pyruvate ratio, is the primary determinant of this association with adverse outcome.
As we might have expected, elevation of the lactate:pyruvate ratio was greater among those children with both metabolic acidosis and raised lactate, compared to those with metabolic acidosis alone[26]. Since metabolic acidosis plus raised lactate was also associated with prolonged requirement for inotropic support and ICU care, as well as decreased survival, it is tempting to suggest a link between elevation of the lactate:pyruvate ratio and these adverse outcomes. However, it is also demonstrated that this metabolic acidosis-hyperlactataemia combination is associated with derangement of other biochemical variables, such as potassium and albumin, which are independently associated with morbidity and mortality. Therefore, although elevation of the lactate:pyruvate ratio is indeed associated with trends towards longer inotrope-dependency and decreased survival in the crude analysis, these tenuous associations must be examined in the light of covariance of the lactate:pyruvate ratio with other biochemical derangements and possible confounders.

One such potential confounder is the use of epinephrine by infusion. Children with metabolic acidosis plus raised lactate were more likely to be receiving epinephrine than those children with metabolic acidosis of other aetiologies. The hypothesis that epinephrine is associated with hyperlactataemia, by binding to skeletal muscle beta adrenergic receptors, increasing production of AMP, and stimulating the Na⁺ K⁺ ATPase, thereby generating ADP, which, in turn, results in increased phosphofructokinase activity, accelerated glycolysis, and a resultant elevation of lactate with a normal lactate:pyruvate ratio, is now widely accepted[22-24, 108].

However, in practice it is difficult to disentangle the effects of epinephrine required for circulatory support, endogenous epinephrine production, and the co-existent effects of hypoperfusion, on the basis of the lactate level alone[22-24, 108]. As in the case of children with post-operative cardiogenic shock, we would expect an apparent discordance between elevation of lactate and the lactate:pyruvate ratio in some children, due to the combination of epinephrine-driven aerobic glycolysis (hyperlactataemias with normal lactate:pyruvate ratio), anaerobic glycolysis due to cellular dysoxia (hyperlactataemia with raised lactate:pyruvate ratio), and depressed glycolysis (normal lactate with raised lactate:pyruvate ratio) occurring at different rates, in different tissues. In these children with septic shock, epinephrine use was not associated with elevation of the lactate:pyruvate ratio, consistent with the phenomenon of accelerated aerobic glycolysis due to exogenous epinephrine.
(normal lactate:pyruvate ratio), rather than anaerobic glycolysis due to hypoxia-ischaemia. Children with elevated lactate:pyruvate ratio had both higher lactate and higher pyruvate levels compared to children with a normal lactate:pyruvate ratio, suggesting a disproportionate rise in lactate (excess lactate, in the terminology of Weil et al), rather than increased oxidative pyruvate consumption[3, 93]. Therefore, it is suggested that this sub-group of children did indeed have occult tissue hypoxia-ischaemia at the net whole body level.

We would expect that elevation of the lactate:pyruvate level would be associated with organ dysfunction, and consequent prolongation of ICU support and increased mortality, on the basis of tissue hypoxia-ischaemia and reperfusion injury[117, 118]. Although the bivariate analysis suggests that the unadjusted odds of survival fall as the lactate:pyruvate ratio increases, it may be more pertinent to ask whether the lactate:pyruvate ratio influences survival in children who are known to have raised lactate. Since metabolic acidosis was nearly universal in children with septic shock, and since the triple combination of metabolic acidosis-hyperlactataemia-normal lactate:pyruvate ratio occurred in more than half of these children, it was possible to examine the association between survival and elevation of the lactate:pyruvate ratio among the sub-group of children with hyperlactataemia. Although the numbers in this sub-group analysis are smaller, with consequent loss of statistical power, it appears that the combination of elevation of the lactate:pyruvate ratio and hyperlactataemia is not associated with worse outcome, compared to children who have a hyperlactataemia with a normal lactate:pyruvate ratio. This finding is borne out by the multivariate analysis, which demonstrates that, after adjusting for lactate (and the co-variables potassium, corrected chloride, and albumin), elevation of the lactate:pyruvate ratio is not associated with altered PICU survival in children with septic shock (odds ratio = 1.0). The implication of this finding is that either hyperlactataemia due to tissue hypoxia-ischaemia is not associated with adverse outcome in children with septic shock, which appears to be counter-intuitive, given what is known about reperfusion injury and the findings of previous authors in relation to the lactate:pyruvate and mortality, or alternatively, that the hyperlactataemia due to hypoxia-ischaemia and the hyperlactataemia due to epinephrine-driven accelerated glycolysis, have equally adverse associations with outcome[68, 87, 96, 118].

However, these findings contrast with those of Levy et al in adults with septic shock, who showed that early mortality was associated with a higher lactate:pyruvate ratio, and with Day and co-workers in adults with malaria, who showed that a higher
Lactate:pyruvate ratio was associated with greater mortality [87, 96]. However, as demonstrated in the study by Levy et al, it may be that serial measurement of the lactate:pyruvate ratio might differentiate survivors from nonsurvivors with greater efficiency [87, 94]. Unfortunately, that question is beyond the scope of this study, since only admission data were collected. The only other study in paediatric septic shock, the pilot study of Dugas and colleagues, is unable to shed more light on the subject, due to small sample size and the lack of any nonsurvivors [93].

Therefore, given the lack of an independent association between the lactate:pyruvate ratio and adverse outcome; the lack of any additional predictive power in the multivariate prognostic model; the practical difficulties inherent in specimen collection; the time factor for pyruvate measurement; and the additional cost, the use of the lactate:pyruvate ratio as a routine tool for prediction of PICU survival in this patient group cannot be recommended. However, in the research setting, the potential uses of the lactate:pyruvate ratio in conjunction with objective measures of cardiac output have yet to be explored in large groups of children with septic shock [93].

This study has several limitations which constrain the interpretation of these findings. The definition of septic shock is a clinical definition that is broadly inclusive, and therefore it is possible, first, that some of the children included in the study group would not have been included if stricter inclusion criteria, such as blood culture positivity, were enforced; and second, that these findings might not apply to homogeneous sub-groups of children with septic shock such as those with meningococcal septic shock [35]. However, on the basis of current evidence, we have no reason to suppose that these findings are not applicable to all children with septic shock, whatever the aetiology. This study has focused on the relationships between lactate, the lactate:pyruvate ratio, morbidity, and mortality in children with septic shock. Ideally, we might wish to compare children with multiple combinations of metabolic acidosis, raised or normal lactate, and raised or normal lactate:pyruvate ratio. However, it must be acknowledged that even the study sample of 83 children with septic shock is not large enough to allow meaningful comparison of such sub-groups with combination acid-base disturbances. A larger, multi-centre study of acid-base disturbance and outcome in septic shock would be required for this purpose.
Conclusion

Elevation of the lactate:pyruvate ratio was common in this group of children with septic shock, in association with moderate-severe mixed metabolic acidosis and both hyperlactataemia and hyperchlaemia. This finding suggests that occult tissue hypoxia-ischaemia was present at the net whole body level in up to one third of children on admission to the PICU.

Children with metabolic acidosis plus raised lactate showed prolonged inotrope- and ICU-dependency, and decreased survival, compared to those children with metabolic acidosis of other aetiology. Although elevation of the lactate:pyruvate ratio was associated with decreased survival in the crude analysis, after adjusting for co-variables, including lactate, potassium, corrected chloride, and albumin, the lactate:pyruvate ratio was not independently associated with changes in PICU survival. Therefore, the hyperlactataemia of hypoxia-ischaemia and the hyperlactataemia of epinephrine-driven accelerated glycolysis might be equally adverse prognostic occurrences. The mechanism underlying the latter effect has yet to be fully explored, particularly in children. Regardless, given the lack of prognostic association with adverse outcome in this study, measurement of pyruvate and calculation of the lactate:pyruvate ratio cannot be recommended as a tool to predict PICU outcome in children with septic shock.
Chapter 6
Summary and recommendations for clinical practice

Post-operative cardiogenic shock
This group of children with post-operative cardiogenic shock following open cardiac surgery had low predicted and observed mortality following open cardiac surgery. In these children, hyperchloreaemia was the predominant acid-base abnormality, whereas primary hyperlactataemic and strong ion gap-driven metabolic acidoses were rare. The presence of a metabolic acidosis per se was not associated with prolonged intensive care dependency. Hypoalbuminemia, an alkalinising force, was associated with a prolonged requirement for inotropic support and intensive care stay. By contrast, hyperchloreaemia was associated with a reduced requirement for epinephrine infusion, supporting the hypothesis that hyperchloreaemia following cardiopulmonary bypass may be a benign phenomenon.

Although metabolic acidosis was mild, or at worst moderate, and due predominantly to hyperchloreaemia, elevation of the lactate:pyruvate ratio was found to be common. Raised lactate:pyruvate ratio was more frequent in children with metabolic acidosis, yet it occurred commonly in children without hyperlactataemia, since elevation of the lactate:pyruvate ratio was due partly to lower pyruvate. Children with raised lactate:pyruvate ratio had longer aortic cross-clamp times and were more likely to receive epinephrine by infusion. However, it was hyperlactataemia, not elevation of the lactate:pyruvate ratio, that was associated with prolongation of inotropic support, mechanical ventilation, and PICU stay.

Therefore, in the setting of mild-moderate metabolic acidosis in children with low predicted risk of mortality following open cardiac surgery, it is suggested that the finding of hyperchloreaemic metabolic acidosis should not prompt escalation of haemodynamic support. By contrast, since hyperlactataemia was associated with prolonged dependence on ICU care, raised admission lactate on admission to PICU should arouse suspicion of low cardiac output syndrome and prompt the clinician to escalate the intensity of monitoring, evaluation of cardiac output indices, and possibly, the level of inotropic support. Since calculation of the lactate:pyruvate ratio did not add useful prognostic information in these children, measurement of pyruvate levels cannot be advocated in this clinical setting. However, these findings should be further investigated, in conjunction with measures of regional and global...
hypoperfusion, in centres with a larger proportion of cardiac surgical procedures in higher operative risk categories.

**Septic shock**

This group of children with septic shock had relatively high predicted and observed mortality rates and demonstrated severe acidaemia, and metabolic acidosis, characterised by hyperlactataemia, hyperchloreaemia, and to a lesser extent, elevation of the strong ion gap. The majority of these metabolic acidoses were of mixed aetiology, with a predominance of lactate- and chloride-driven metabolic acidosis. Severe hypoalbuminaemia provided a clinically significant positive contribution to the net observed base excess, resulting in underestimation of the true magnitude of the underlying metabolic acidosis.

In a multivariate logistic regression model, after adjusting for weight, the admission lactate, potassium, corrected chloride, and albumin levels were independent predictors of survival in these children. The model using admission biochemical parameters had good predictive power, but has yet to be validated in an external data set. In this prognostic model, elevated lactate, elevated potassium, decreased albumin, and, contrary to the original hypothesis, increased corrected chloride, were associated with lower relative odds of survival. Elevated strong ion gap was not independently associated with either PICU outcome, or PICU dependency, a finding that supports a benign view of this acid-base disturbance.

Elevation of the lactate:pyruvate ratio was also common, suggesting occult tissue hypoxia-ischaemia was present at the net whole body level in up to one third of children on admission to the PICU. Children with metabolic acidosis plus raised lactate showed prolonged inotrope- and ICU-dependency, and decreased survival, compared to those children with metabolic acidosis of other aetiology. However, after adjusting for co-variables, the lactate:pyruvate ratio was not independently associated with PICU survival. Therefore, the hyperlactataemia of hypoxia-ischaemia and the hyperlactataemia of epinephrine-driven accelerated glycolysis might be equally adverse prognostic occurrences in this setting.

It is suggested that the base excess should not be used to assess the severity of metabolic acidosis in children with septic shock, unless the alkalinising effect of hypoalbuminaemia is taken into account. However, in contrast to the scenario of post-operative cardiogenic shock, the finding of metabolic acidosis either due to
raised lactate, or raised chloride, should prompt the clinician to increase levels of monitoring, and lower the threshold for escalation of haemodynamic or renal support, in children with septic shock. The finding of metabolic acidosis due primarily to elevation of the strong ion gap should prompt efforts to identify the source of the 'unmeasured' anions, but does not necessarily indicate a need to escalate therapy. Given the lack of prognostic association between the lactate:pyruvate ratio and adverse outcome, measurement of pyruvate cannot be recommended as a tool to predict PICU outcome in children with septic shock. These findings should be tested, in conjunction with measurement of cardiac output indices, in studies of serial lactate and pyruvate levels after intensive care admission.
References


69. Li J, Schulze-Neick I, Lincoln C, Shore D, Scallan M, Bush A, Redington AN, Penny DJ: Oxygen consumption after cardiopulmonary bypass surgery in


85. Hannam RL, Ybarra MA, White JA, Ojito JW, Rossi AF, Burke RP: Patterns of lactate values after congenital heart surgery and timing of


### Appendix 1: Equations and Definitions

<table>
<thead>
<tr>
<th>Metabolic acidosis</th>
<th>Standard bicarbonate &lt; 22 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard bicarbonate</strong></td>
<td>$0.23 \times 5.33 \times \text{antilog}[(\text{pH} - 6.161)/0.9524]$</td>
</tr>
<tr>
<td><strong>BE</strong></td>
<td>$0.5 \times (8 \times a - 0.919)/a + 0.5 \times ((0.919 - 8 \times a)/a)^{1/2} - 4 \times (24.47 - \text{standard bicarbonate}/a)$</td>
</tr>
<tr>
<td>where $a^*$</td>
<td>$0.00404 + 0.000425 \times \text{haemoglobin}$</td>
</tr>
<tr>
<td>Corrected chloride (cCl)</td>
<td>$140 \times \text{Cl} / \text{Na}$</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>cCl &gt; 110 mmol/L</td>
</tr>
<tr>
<td>Raised lactate</td>
<td>&gt; 2 mmol/L</td>
</tr>
<tr>
<td>Raised strong ion gap (SIG)</td>
<td>&gt; 2 mmol/L</td>
</tr>
<tr>
<td>Low albumin</td>
<td>&lt; 30 g/L</td>
</tr>
<tr>
<td>SIDc</td>
<td>Na + K + Ca + Mg - (Cl + lactate)</td>
</tr>
<tr>
<td>SIDe</td>
<td>Bicarbonate + PO4 charge + albumin charge</td>
</tr>
<tr>
<td>SIG</td>
<td>SIDc - SIDe</td>
</tr>
<tr>
<td>$[\text{BE (alb)}]$</td>
<td>$(0.123 \times \text{pH} - 0.631) \times (42 - \text{albumin})$</td>
</tr>
<tr>
<td>$[\text{BE (fw)}]$</td>
<td>$0.3 \times (\text{Na} - 140)$</td>
</tr>
<tr>
<td>$[\text{BE (cl)}]$</td>
<td>$108 - \text{Cl}$</td>
</tr>
<tr>
<td>$[\text{BE (lact)}]$</td>
<td>$1.5 - \text{lactate}$</td>
</tr>
<tr>
<td>Albumin</td>
<td>42 g/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>140 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>108 mmol/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.5 mmol/L</td>
</tr>
</tbody>
</table>

*Calculated by Radiometer ABL 520.*