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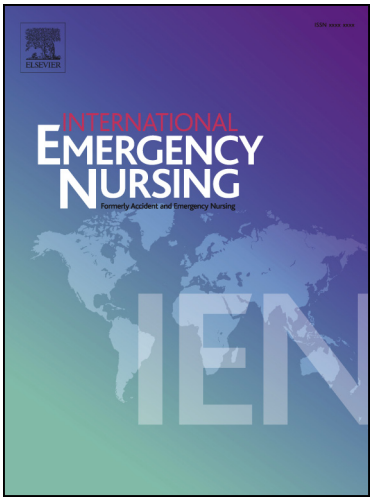

Is Lactate an Effective Clinical Marker of Outcome for Children with Major Trauma? – A Literature Review

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IS LACTATE AN EFFECTIVE CLINICAL MARKER OF OUTCOME FOR CHILDREN WITH MAJOR TRAUMA? – A LITERATURE REVIEW

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ABSTRACT

Introduction

The assessment and treatment of children with major injury is fraught with difficulty – differences in anatomy and physiology mean that children that have suffered trauma can be over or under assessed. In recent years, there has been an increase in the use of biochemical markers to assist the clinician in determining severity of injury. This paper examines the evidence in both adult and paediatric trauma in the use of lactate is a marker.

Method

A literature search was completed on Medline, CINAHL, Ovid and Science. 63 papers were initially identified - 41 papers were rejected after reading the abstracts. Of the 22 remaining papers - 6 had a paediatric focus, 16 were adult – of these 12 were rejected as not primary studies. 10 papers were fully critically reviewed.

Results

The literature shows that an elevated lactate in a trauma patient is strongly correlated to severity of injury, length of stay and morbidity and mortality. However, one elevated lactate maybe misleading and that lactate clearance - that is when lactate levels return to normal, is just as important in the assessment of the severely injured. However, from this paper it is clear that there is very little evidence in the relation children and lactate and that more studies need to be completed.

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INTRODUCTION

Major trauma in children in the United Kingdom is relatively rare. In 2012 4,720 children were admitted to Emergency Departments suffering with multiple trauma, of these 737 were severely injured with a Injury Severity Score (ISS) of greater than 15 (TARN 2012). Major trauma morbidity and mortality surpasses all major disease in children and young adults. It could be argued that trauma is the most serious public health and health care problem in this population (American College of Surgeons 2012).

The differing anatomy and physiology in children can pose challenges for clinician faced with a child suffering major trauma. Children have an increased physiological reserve of blood, which allows for maintenance of systolic blood pressure even when 30% of the circulating blood volume has been lost (American College of Surgeons 2012). Other vital signs, heart rate, capillary refill and respiratory rate can be altered due to psychological, and environmental factors and not due to blood loss, calling into question their sensitivity. This can lead to the child being incorrectly assessed as to the severity of their injuries, and either be over or under resuscitated, neither an ideal outcome (Shah et al 2013)

Recent military conflicts led to considerable advances in the care of the severely injured adult. In particular, our understanding of the coagulaopathy of haemorrhage, its' control and management, and importantly, the use of biochemical markers as an indicator of the severity of shock.

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Lactate is one such biochemical marker and is available in routine arterial and venous blood gases. Kruse et al (2011) completed a systematic review of the literature surrounding the measurement of lactate, via differing routes. They concluded that a peripheral venous lactate demonstrated a good correlation to arterial lactate, as well as a very high sensitivity and acceptable specificity for hyperlactaemia. There was conflicting evidence surrounding the use of capillary lactate as there is a tendency for a higher lactate to be measured via this route, however the number of studies reviewed were small in nature, but they recommend that a higher lactate level is set for a capillary gas. Lactate is known to be a by-product of anaerobic metabolism and it has been suggested that an increase in the traumatized adult can be an indicator of occult hypoperfusion and occult bleeding (Cheddie et al 2013). This paper will firstly discuss the production of lactate in trauma, and the evidence surrounding lactate as a marker of occult bleeding. It will also discuss the application of the evidence to children.

THE BIOCHEMISTRY OF LACTATE PRODUCTION

Since the 19th Century lactic acid was known to have been formed as a result of lack of oxygen to the cells, and was first discovered with the fermentation of lime beans in anaerobic conditions (Pasteur 1863 cited in Brooks 2009). Lactate acid is generated in cells under anaerobic glycolysis. Glycolysis is a complex process converting a glucose or glycogen molecule into energy. The process uses different enzymes at differing stages to generate Adenosine Diphosphate (ADP), from Adenosine Triphosphate (ATP). ADP and ATP are

the energy molecules required for bodily functions. The end product of glycolysis is pyruvate.

Pyruvate can have two fates, if there is sufficient oxygen it enters the Kreb's cycle where it is metabolized further and produces more ADP and ATP. If there is insufficient oxygen the pyruvate gets convert into lactate via lactate dehydrogenase (LDH) (Sola-Penna 2008). This is a reversible process and when there is sufficient oxygen, lactate can be converted back to pyruvate and enter the Kreb's cycle to generate more energy (Agrawal et al 2004). However, if hypoxia continues this leads to an accumulation of lactate and ultimately lactate acidosis. See Figure 1

Lactate Production in Children

It is unclear if the biochemistry of lactate production is the same in children. Exercise studies in children (Mocellin et al 1991 cited by Ramanathan et al 2015) showed a poor correlation between an increased lactate and anaerobic metabolism. During exercise, children have a higher oxygen transport capacity, thereby, suggesting that they have a differing physiological response to tissue hypoxia (Anderson and Mahon 2007). It is not clear how this mechanism affects a child's ability to respond to hypoxia due to hypoperfusion.

Aono et al (1993) suggest that fear and anxiety may also cause an elevated lactate. In a small study (n= 28 males aged 2 years), Aono et al (1993)

examined the lactate levels between 2 differing sets of children (calm vs. upset) undergoing anaesthesia for circumcision. The study showed a correlation between higher lactic acid and crying (p <0.001). Aono et al (1993) suggest this rise in lactate is due to the release of stress hormones, when the child is crying. However, the authors did not measure the level of stress hormones or when the lactate level reduced to normal. Although this study is small, it does raise an interesting point that an increased lactate in a child with severe trauma may be due to fear and anxiety rather than haemorrhage. What is clear is that there is very little specific knowledge about the production and clearance of lactate in children during trauma, and how their bodies respond to the increase in lactate and the subsequent acidosis.

METHODOLOGY OF LITERATURE SEARCH

In order to examine this area further, initially a research question was developed using a PICO model as a structured approach (Khan et al 2011). From each of the components of the research question a list of keywords was developed including synonyms with spelling variations (see table 1). These keywords were used in differing computer search engines – for example, Medline, CINAHL, Ovid and Science. Both paediatric and adult populations were included to ensure that as wide a search possible was completed. The literature search was restricted to the English language, peer-reviewed journals and from the 2000-2015, these dates were used to ensure that recent literature pertinent to lactate was reviewed.

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Table 1:

Keywords used
Lactates Lactic acid Acidosis, lactic L-lactate dehydrogenase/or lactate dehydrogenase Blood Lactate Levels Hypoperfusion Hypovolaem* shock H*emorrhage Blood loss Bleeding P*ediatric Major, trauma

The abstracts of the literature were reviewed for their relevance and inclusion. The inclusion criteria, for this review were child and adult trauma, lactate levels, and outcome, both pre-hospital and hospital literature was included. Articles that focused on lactate in sepsis were rejected, due to the differing pathophysiology of disease. The literature was reviewed and categorized according to themes. The themes that emerged were single lactate levels and outcome, and lactate clearance and outcome..

Results

Sixty-three papers were identified, and from reviewing the abstracts 27 papers, met the inclusion criteria, and full text papers were obtained. Five papers were rejected as opinions, letters and case studies. Of the remaining papers (n=22), 6 were paediatric papers and 16 were adult papers. Of the 6 paediatric papers, 5 were rejected as not relevant to topic area but added to the body of knowledge. Of the 16 adults papers 7 were rejected due to

relevance, systematic reviews and non-trauma papers, again these were reviewed to add to the body of knowledge. See Figure 2.

The remaining paper (n=10) was reviewed using the Oxford Centre for Evidence-based Medicine – level of evidence (2009) and the CASP Cohort Appraisal tool (2010). The papers were further classified as papers on single elevated lactate marker (n=6) and lactate clearance (n=4). See table 2.

LACTATE IN TRAUMA - THE EVIDENCE

Over the last decade it has been recognized that in trauma, patients suffer from the 'blood vicious triad' of acidosis, hypothermia and coagulopathy (Cosgriff et al 1997). This has led to a greater focus on the measurement of local or systemic markers of metabolic acidosis as an indicator of severity of injury, and to monitor treatment efficacy, and to provide prognostic information (Sharon and Scalea 1999). There are a number of biochemical markers that indicate acidosis, lactate levels are easily obtained and the most commonly used serum marker. Lactate level is now commonly considered as a proxy marker for the severity of injury (Martin et al 2006), compared to other markers of acidosis such as base deficit (Smith et al 2001, Husain et al 2003). Elevated lactate levels are not universally defined, however for this paper a normal lactate levels as <2.0mmols/L, and high lactate levels as >4.0 mmols/L (Anderson et al 2013).

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Lactate as a biochemical marker.

Paladino et al (2008) argue that relying on vital sign as the only indicator of haemorrhage, and therefore potential major trauma, is relatively insensitive. From their study they suggest that the addition of a lactate can aid the clinician in determining major injury. Paladino et al (2008) completed a retrospective study of 1435 patients(age > 13 years) and of this sample, 242 (17%) had major injuries. They defined major injuries as those patients that received blood transfusion, a drop in hematocrit of greater than 10 points in the first 24 hours or an injury severity score (ISS) of > 15. They found that using traditional vital signs, of heart rate, blood pressure was poor at identifying major injury (sensitivity of 40.9% CI 95%). They also found that lactate was higher ($p < 0.01$) in the major injury patient. Paladino et al (2008) go on to suggest that lactate at a level of 2.5 mmol/l was most efficient at differentiation major from minor injuries (sensitivity of 76% and specificity of 49%). This study suggests that the addition of a lactate level in the assessment of the injured patient can help to identify those patients with major injuries. However, the exclusion category included those patients that went immediately to theatre, therefore by definition must have been seriously unwell, and consequently may have depressed the results of only examining the abnormal vital signs.

Martin et al (2006) completed a retrospective review of all adult patients on a surgical intensive care unit. The study compared base deficit and lactate as a predictor of mortality and length of stay (LOS). Of the sample (n=1,298 patients) - 1,026 were trauma patients. Lactic acidosis was present in 41% of

all patients and a raised based deficit in 52% of all the patients. Martin et al (2006) found that both lactate (95% CI) and base deficit (95% CI) could be use to predict mortality on admission ($P < 0.01$). However, increased lactate levels predicted mortality and an increase LOS regardless of the base deficit levels ($P < 0.01$) – where as an increased base deficit level had no predictive value if lactate levels were normal ($P = 0.97$). From their study Martin et al (2006) suggest that lactate is a more sensitive biochemical marker of predictive outcome or mortality, morbidity and LOS. Within the population studied, both illness and injury were included in the sample size. It is difficult to determine if the results would be different if the study only focused on trauma patients, and therefore the results should be treated with caution for the trauma population.

Cheddie et al (2013) completed a small-scale study (n = 28 adult patients) identifying the correlation between base deficit, lactate and injury severity with the development of early-onset coagulopathy and mortality. They found that base deficit ($P = 0.011$) was a more sensitive maker of coagulopathy than lactate ($P = 0.10$). However, they do suggest that an increase in lactate production arises from anaerobic metabolism as a consequence of hypoperfusion, most commonly due to haemorrhage. Whilst base deficit is an important biochemical marker of coagulopathy, lactate is more sensitive indicator of haemorrhage, and therefore potential hypoperfusion. However, due to the small sample size (n=28) it is difficult to generalize these findings to the wider trauma population.

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Oullett et al (2010) retrospective study of adult trauma patients with blunt injury and an ISS of greater than 12 provided further evidence to support the theory that lactate is an indicator of mortality and LOS. The study examined the correlation between lactate acid level, mortality and length of stay in days (LOS). A correlation was found between increase level of lactate on admission and mortality ($P < 0.0001$) and LOS ($P < 0.0001$). As a retrospective study, this could be associated with selection biases, also they included all patients that had an ABG within 2 hours of arrival. This time delay raise the question about how much resuscitation that the individual had prior to the ABG being taken, and how this could positively or negatively affect the results. Although there are a number of limitations Oullett et al (2010) highlight a correlation between raised lactate and outcome in adults, including increased mortality and morbidity and LOS.

In another retrospective study of 360 adult patients that had suffered blunt trauma, arterial blood gases were compared to the results of computed tomography (CT) scan (Vohara and Paxton 2013). They found that patients with a major injury identified on CT scan generally had a statistically higher mean lactate level that those without major injury (chest injury – mean lactate level with negative 2.36 vs. positive 2.90 $P = 0.03$, abdominal and pelvic injury – mean lactate with negative 2.36 vs. positive 3.18 $P = 0.01$).

This suggests that the initial lactate level is important in predicting morality, morbidity and LOS in the severely injured adult patients, Given that the population study were adults the applicability to children is unknown.

Ramanathan et al (2015) completed a prospective study on the predictive value of admission lactate in paediatric trauma. All children 15 years and under (n=277) that had a trauma call and an admitting lactate level, were included. They found that there was a positive correlation between elevated lactate and a higher ISS (12.8 vs. 4.6, p = <0.00001). They also found that a lactate of 4.7 mmol/L approximated an ISS of 15 i.e. severe injury (ISS = 1.87 + 2.78 lactate). From their study Ramanathan et al (2015) found that a lactate less than 2.0mmol/L indicated that the child had no injuries, however the gap between 2.00 mmols/L and 4.7 mmols/L was indeterminate in its predictive potential for injury or outcome.

The interpretation of a single lactate level maybe misleading, lactate clearance, may represent a better indicator of ongoing tissue hypoperfusion and therefore, maybe a better guide to the resuscitation of the trauma patient (Odom et al 2012).

Lactate Clearance

Lactate clearance is the rate of fall in lactate after resuscitation has started (Munde et al 2014). Studies (Manikis et al 1995, Husain et al 2003, Regnier et al 2012, Odom et al 2012) all suggest that not only blood levels on admission or highest blood lactate are important in determining morbidity and mortality, but also the duration of hyperlactaemia, i.e. raised lactate in the blood stream, and this is related to posttraumatic complications. It is assumed that a decrease in lactate clearance may represent prolonged

cellular hypoxia, which is the presumed mechanism for end-organ damage (Odom et al 2012), although this mechanism is not clearly defined.

There is conflicting evidence in the literature regarding the length of time for lactate clearance to be of significance. In an early study, Manikis et al (1995) completed a investigation on the correlation of lactate and mortality on 129 adult trauma patients. They examined the blood lactate every 3 hours until they normalized. They found that both initial lactate and the highest lactate levels were higher in non-survivors than in the survivors ($P < 0.5$). They also found that 'lactime' in days, was greater in non-survivors (2.2 days) compared to survivors (1.6 days) ($P < 0.01$). There is no definition with the paper as to what 'lactime' was – making interpretation of the results challenging. However, they concluded that level of lactate and the duration of lactate acidosis was related to post-traumatic complications.

Regnier et al (2012) calculated blood lactate levels and lactate clearance within their study of 586 patients. They focused on the initial lactate levels and lactate levels at 2 hours (n=373 64%). Within their study Regnier et al (2012) found that initial blood lactate (AUC 0.84, 95% CI: 0.77-0.90, $P < 0.001$) and lactate clearance (AUC 0.75, 95% CI: 0.66-0.82, $P = 0.001$) were significant predictor of early death. They also found that initial blood lactate (AUC 0.61, 95% CI: 0.55-0.65, $P < 0.001$) and lactate clearance (AUC 0.59, 95% CI:0.54-0.64, $P = 0.001$) were also predictors of an ISS of more than 15. They argue that in trauma patients there is a need for rapid assessment and resuscitation, and that the diagnosis of occult hypoperfusion must be made early – delaying

the assessment of lactate clearance for 6 to 24 hours could be detrimental to the patient. From their findings they suggest that early (0 – 2 hours) lactate clearance is an important and independent prognostic variable of outcome. However, this study was completed on adult patients (age = 37 +/- 15), it is unclear how applicable these findings are with children and their compensatory mechanisms. Regniers et al (2012) only review lactate levels up to 4 hours, where another study (Odom et al 2012) suggest that 6 hours is more acute reflection of lactate clearance.

Odom et al (2012) study examined adult trauma patients (n=269) with severe injuries (ISS > 20). They were specifically examining lactate clearance over 6 hours. They describe lactate clearance as:

Initial lactate – current lactate x 100/ Initial lactate

A positive value demonstrates clearance of lactate, whereas a negative value denoted an increase in lactate after intervention. Odom et al (2012) found that a initial lactate of 4.0 mg/dL or greater, had a mortality within the sample size of 18.8% (95% CI: 15.7-21.9%). For lactate clearance of 60% or greater, 30% to 59%, and less than 30%, the odds ratio for death were 1.0, 3.5 (95% CI: 1.2-10.4), and 4.3 (95% CI: 1.5 – 12.6) respectively. In essence, they found that lactate clearance at 6 hours was strongly associated with mortality, and as lactate clearance fell, mortality increased. This suggests that lactate clearance is an independent predictor of death in a broad cohort of trauma patients.

Husain et al (2003) defined 'clearance time' as the time of the first normal lactate level that was recorded. They divided their adult trauma sample (n=137) into 4 groups. Group 1 never achieved normal lactate levels, group 2 normalized lactate within 24 hours, group 3 achieved normal lactate between 25 to 48 hours and group 4 took longer than 48 hours. Group 1 – those who had never achieved normal lactate levels had a mortality rate of 67%, whereas those patients that cleared lactate in less than 24 hours, had a 10% mortality rate. They suggest that both the initial lactate (P = 0.05) and clearance times (P <0.001) were found to be significant in predicting patient outcome at discharge. Consequently the best change of survival occurs when resuscitation efforts results in lactate clearance to normal values within 12 to 24 hours.

A review of these studies suggest that the biochemical marker of lactate can be use by clinicians to assist in the assessment of the severely injured patients, as it could be an indicator of hypoperfusion and therefore guide resuscitation.

It is emphasized that clinicians should also ensure that clinical judgment is also used when assessing patients (Paladino et al 2008, Oullett et al 2010). Other Studies (Husain et al 2003, Odom et al 2012) have suggested that the clearance of lactate be it 2 hours, 4 hours or 24 hours, is an important predictor of mortality and morbidity and again should be used to guide the initial treatment plan.

LACTATE AND PAEDIATRIC TRAUMA

All but one (Ramanathan et al 2015) of the studies discussed in this paper have an adult trauma population. From this adult population it is clear that an initial raised lactate was important in predicting mortality and morbidity (Martin et al 2006, Cheddie et al 2013, Oullett et al 2010, Vohara and Paxton 2012). However, a single lactate reading maybe misleading (Manikis et al 1995, Husain et al 2003, Regnier et al 2012, Odom et al 2012). Of concern is the applicability of these studies to the paedatric population. Ramanthan et al (2015) study in injured children showed that a lactate of over 4.7 mmols/L, was strongly suggestive of severe injury in children. However, lactate between 2.0 and 4.7 mmols/L remained indeterminate in predictive potential for injury or outcome. From this one study it is difficult to determine if high initial lactate levels and lactate clearance is an indicator of outcome in paedatric trauma, as it is in the adult trauma population.

Primary research in children presents a number of specific challenges. In many areas of study, primary research is completed on adults and then applied to children. For some areas this is acceptable and reasonable. However, in the area of trauma, children's compensatory mechanism and physiology may mean that research on adults may not be as applicable, leaving children to be seen as being 'therapeutic orphans' (Allmark 2002) in trauma management. Given the paucity of paediatric specific evidence future research is needed on the effectiveness of lactate as a clinical marker of outcome for children with major trauma.

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Conflicts of Interest: none

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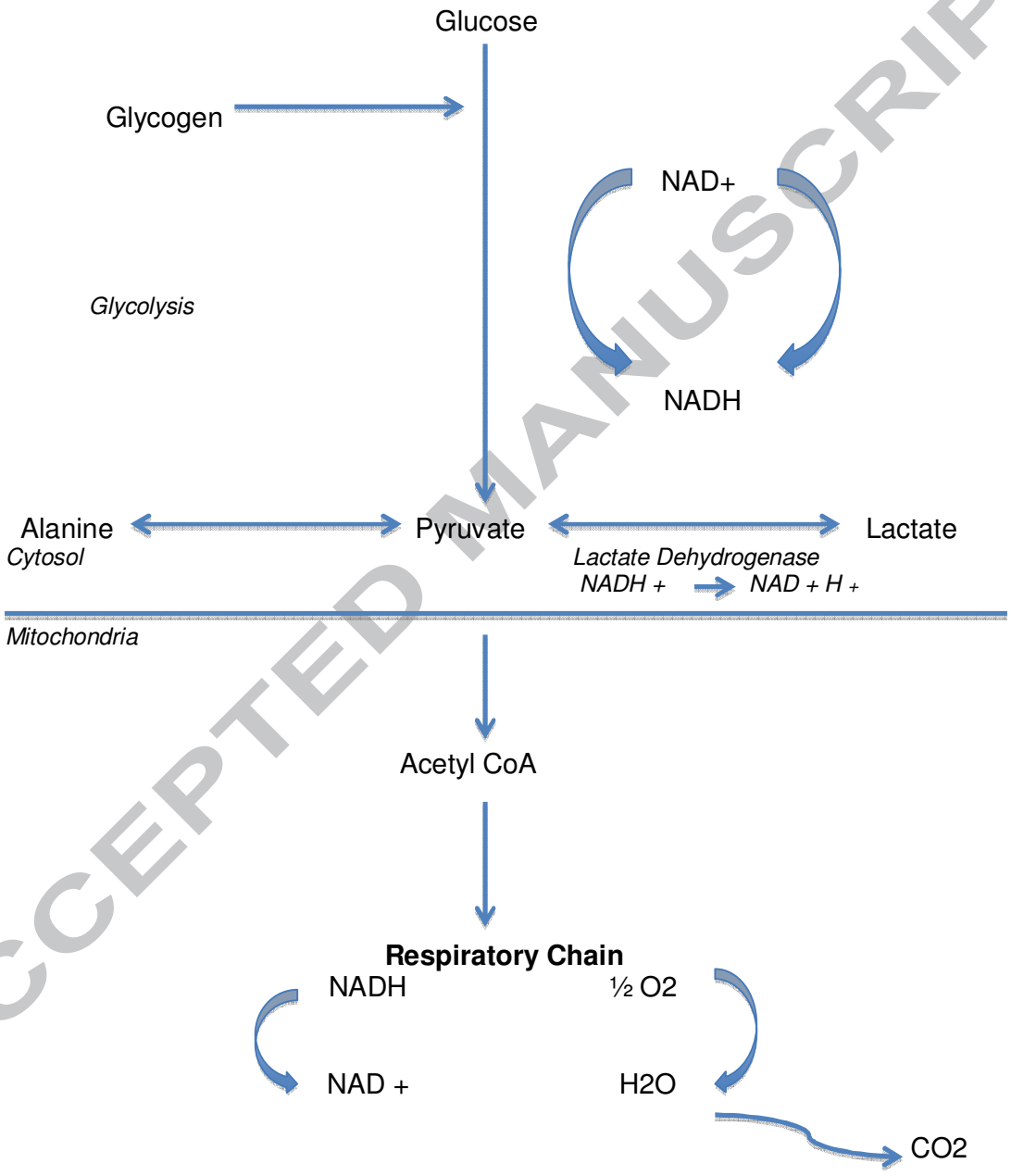
Figure 1 **Biochemistry of Lactate Production**



Adapted from: Agrawal et al (2004)
Pictorial diagram of glycolysis and the production of lactate at cellular level.

Figure 2 **Flowchart of Literature Search**

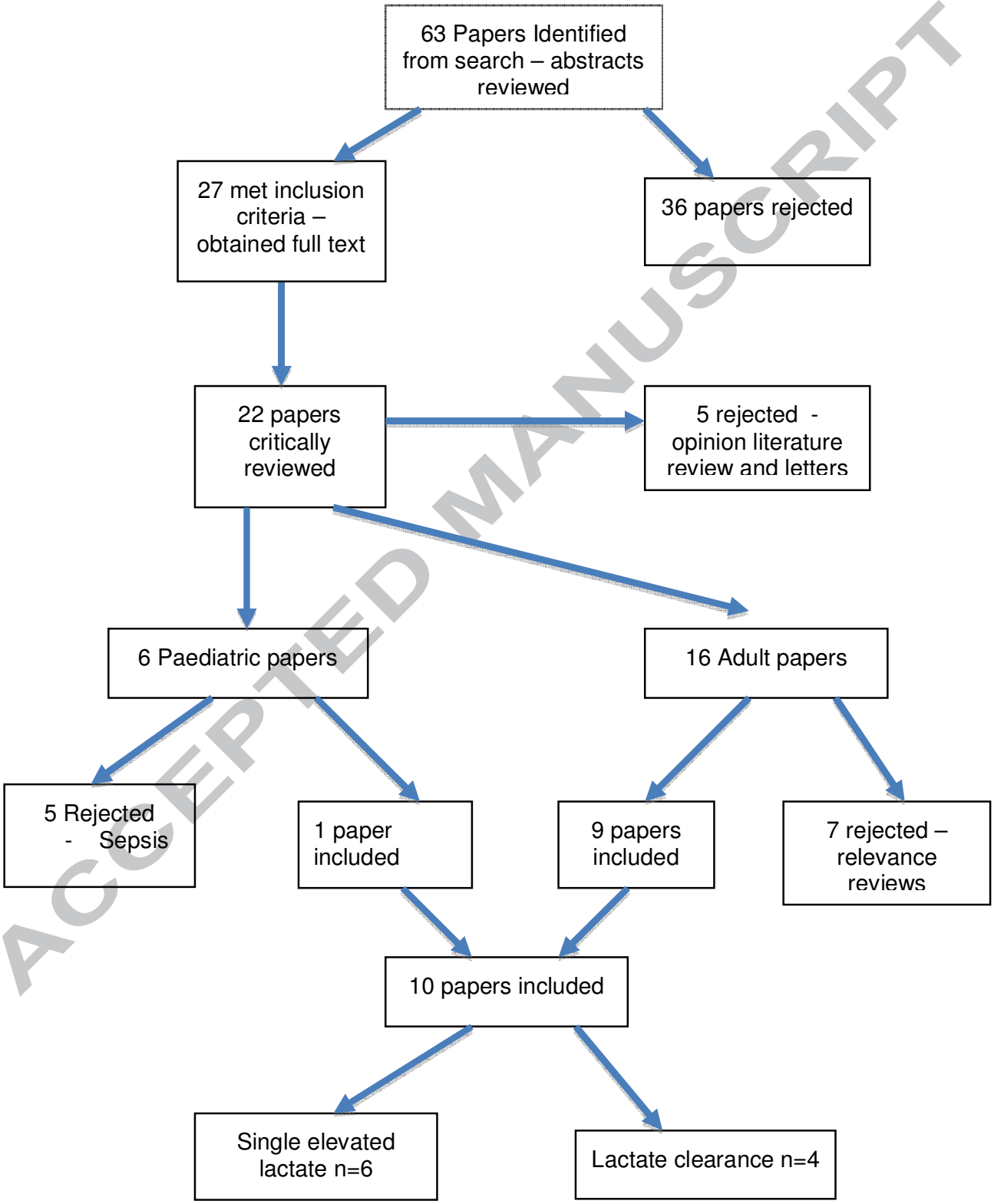


Table 2 Literature Obtained and Reviewed:

Author(s)	Year	Methodology	Sample (n =)	Recommendations
Cheddie et al	2013	Retrospective chart analysis – adult trauma patients -	N = 28	Raised lactate not correlated to the development of coagulopathy in trauma
Husain et al	2003	Retrospective reviews of surgical intensive care adult patients -	N=137	Elevated initial and 24 hour lactate levels are significantly correlated with mortality.
Manikis et al	1995	Retrospective review of adult patients admitted with trauma	N= 129	Serial lactate measurements are reliable indicator of morbidity and mortality after trauma.
Martin et al	2006	Retrospective review of intensive care adult patients – trauma and surgical -	N= 1,298	Elevated lactate and prolonged clearance may be used to identify lactic acidosis and predict mortality on admission.
Odom et al	2012	Retrospective cohort study over 10 years – adult trauma patients	N = 4,742	Both initial lactate and lactate clearance at 6 hours independently predict death in trauma patients
Ouellet et al	2012	Retrospective cohort study – adult blunt trauma patients	N=2,269	Statistically significant association between lactate on arrival and both mortality and length of stay
Paladino et al	2008	Retrospective review of prospective	N=242	The addition of lactate to triage vital signs increases the ability to

		collected data - adult trauma centre		distinguish major from minor injury.
Reginer et al	2012	Prospective observational cohort study – adult patients	N= 586	Early (0-2 hours) lactate clearance is an important and independent prognostic variable that should probably be incorporated in future decision schemes for the resuscitation of trauma patients
Vohara and Paxton	2012	Retrospective chart review – adult patients	N=360	Lactate can be elevated in the trauma patient with no occult injuries
Ramanathan et al	2015	Prospective review – paediatrics trauma patients	N=227	Elevated venous lactate it associated with injury & outcomes. Lactate over 4.7mmols/L is strongly suggestive of severe injury, and lactate below 2.0mmol/L reassuring as not having injury. Not clear between these two figures.

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Highlights

- Children attending ED in the UK with major trauma are rare – however the assessment of these children are difficult.
- The use of lactate as a marker of hypoperfusion has be used in adult trauma care for a number of years
- There is evidence to show that a raised lactate is correlated to morbidity and mortality in the adult trauma victim
- There also evidence to show that there is a correlation between lactate clearance and outcome
- There is very little evidence to show if this evidence is applicable in children

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Conflicts of Interest: None

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Keywords: lactate, elevated lactate, lactate clearance, paediatric, trauma, haemorrhage