**Clinical question.**

NRP 021B - In neonates requiring resuscitation and not responding to CPR (P), does the administration of sodium bicarbonate (I) versus no bicarbonate (C) improve outcome (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis:** Intervention/therapy.

**State if this is a proposed new topic or revision of existing worksheet:** Revision

**Search strategy (including electronic databases searched).**

Ovid, Medline from 2004-2008

Mesh terms Neonates and/or resuscitation and/or CPR and sodium bicarbonate and/or asphyxia and/or infant and/or delivery room. Relevant hits: infant and/or newborn and bicarbonate (17 hits), sodium bicarbonate and delivery room + resuscitation (165 hits), sodium bicarbonate + delivery room (4 hits) - Two new studies retrieved. Embase from 2004 to 2008

Same terms and combinations – same two studies retrieved, Cochrane library – one study found, ECC endnote library – no new study found.

**State inclusion and exclusion criteria**

All neonatal studies related to sodium bicarbonate administration during cardiac arrest. Animal studies were included. All English language studies included if published in full. Editorials, abstracts, consensus statements were excluded. Selected adult studies were included.

**Number of articles/sources meeting criteria for further review:**

3 neonatal human studies, 6 neonatal animal studies, 3 adult human studies (including 1 review), 15 adult animal studies

LOE 1
LOE 2
LOE 3
LOE 4
LOE 5

**Summary of evidence**

### Evidence Supporting Clinical Question

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A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint
B = Survival of event  D = Intact neurological survival
* = overlapping patients

Normal text = adult studies
Bold = neonatal studies
Italics = Animal studies
Bold italics = neonatal animal studies
### Evidence Neutral to Clinical question

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#### Key:
- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

* Italics = Animal studies
  - Normal text = adult studies
  - **Bold** = neonatal studies
  - **Italics** = Animal studies
  - **Bold italics** = neonatal animal studies

### Evidence Opposing Clinical Question

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#### Key:
- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

* Italics = Animal studies
  - Normal text = adult studies
  - **Bold** = neonatal studies
  - **Italics** = Animal studies
  - **Bold italics** = neonatal animal studies
In the context of resuscitation in adults the use of sodium bicarbonate was introduced in the 1960s based on the following logic. Acidosis is a common accompaniment to cardiac arrest; acidosis impairs heart muscle function; the presence of acidosis impairs the action of adrenaline; therefore reversal of acidosis by the use of sodium bicarbonate might be helpful.

In resuscitation of infants at birth the background is slightly different. Newborn mammals are known to survive asphyxia for considerably longer than older members of the same species and there is a direct relationship between this survival time and the pre-asphyxial glycogen concentration in the cardiac ventricles (Dawes 1959 p516, Stafford 1960, p153 - LOE5). The ability of the newborn heart to maintain a circulation in the absence of oxygen for a longer period than the adult is due to its ability to produce energy by anaerobic glycolysis (Dawes 1963 p43 – LOE5). If this is prevented, by injection of sodium iodoacetate, the circulation in rats fails as quickly in the newborn as in the adult (Himwich et al 1942 referred to in Dawes 1959 p516).

Numerous early physiological experiments with asphyxiated newborn mammals showed that administration of alkali and glucose prolonged survival and facilitated resuscitation, presumably by both maintaining a biochemical milieu suitable for glycolysis and provision of a suitable substrate.

The role of sodium bicarbonate during resuscitation remains controversial. There are concerns that in the absence of adequate ventilation, administration can exacerbate intracellular hypocarbia thus worsening intracellular acidosis. Moreover as a secondary consequence either directly or indirectly, there may be impaired myocardial function. In the premature infant infusion of sodium bicarbonate has been associated with the development of intraventricular hemorrhage (Simmons 1974 p6, LOE 5). However, this paper has many flaws and there are other more likely explanations for its findings.

There is a small randomized neonatal study in “asphyxiated “ term infants (low five minute Apgar score and still receiving bag/mask positive pressure ventilation) that failed to demonstrate any beneficial effect of sodium bicarbonate administration on neurologic outcome or survival (Lokesh 2004 p219, LOE 2). A recent study failed to demonstrate any benefit from sodium bicarbonate administration on acid-base status in the 24 hours following infusion (Murki 2004 p696, LOE2). However, neither of these endpoints are of particular interest in the context of resuscitation at birth. It is important to note that the patient population of these two studies is the same, but the endpoint is different.

A number of neonatal animal studies in asphyxiated newborn animals taken beyond the ‘last gasp’ (Adamsons 1963 p697, 1964 p807; Dawes 1963 p167 and 1963 p43, Daniel 1966 p562 – all LOE 5) show a beneficial effect of various bases, including sodium bicarbonate, if given together with glucose. Such benefits in monkeys include a rise in blood pressure and a return of gasping (Daniel 1966 p562, LOE 5).

A tangential neonatal animal study has noted attenuated hemodynamic responses to resuscitation with epinephrine and oxygen when concomitant acidosis was present (Preziosi 1993 p1901, LOE 6). However this model used a pure metabolic acidosis rather than the mixed acidosis noted in intrapartum asphyxia. Acidosis was produced by the infusion of exogenous lactate, which may not adequately simulate acidosis derived from intracellular acid production due to cellular hypoxia. Additional neonatal studies suggest that bicarbonate administration increases arterial pH, brain intracellular pH and PaCO2 without producing concomitant paradoxical brain intracellular acidosis provided adequate cardiac output is maintained (Sessler 1987 p817, Laptook 1985 p815, both LOE 5).

One neonatal human study reported significant reduction in cerebral blood flow (up to 50%) following bicarbonate infusion (Lou 1978 p239, LOE 5). However, this study did not involve babies needing resuscitation and used infusions of bicarbonate at dosages considerably greater than those recommended for resuscitation at birth.

An evidence-based review of adult human and animal studies indicates that no human study has demonstrated a beneficial impact on survival and that several adult human studies (LOE 3 and 4) demonstrated deleterious effects on physiologic endpoints from the administration of bicarbonate during CPR (Levy 1998 p457). A number of neonatal animal studies have demonstrated a benefit of administration of base during resuscitation (Adamsons 1963 p697 & 1964 p807, Dawes 1963 p167 and 1963 p43, Daniel 1966 p526 – all LOE 5). Some adult animal studies have also demonstrated a similar benefit (Bar Joseph 1998 p1397, Bleske 1992 p525, Leong 2001 p309, Vukmir 1995 p515 – all LOE 5). However, several adult animal studies have also demonstrated impaired function in response to bicarbonate administration during CPR (Guerci 1986 p75, Wiklund 1990 p430, Kette 1991 p2121, Federiuk 1991 p1173, Rubertsson 1993 p1051, Neumar 1995 p249 - all LOE 5).

A number of deleterious side-effects of sodium bicarbonate administration have been demonstrated in adult animal studies. However, the benefit from the use of sodium bicarbonate in neonatal animal studies appears to be its ability to prolong the gasping phase that follows primary apnoea (Adamsons 1963 p 697 & 1964 p807, Dawes 1963 p167 and p43- all LOE 5) and, perhaps more importantly, to ‘restart’ the gasping phase and improve heart rate and blood pressure if administered after the last gasp (Daniel 1966 p526 LOE 5). This effect is highly relevant. Certainly this data requires further investigation and these studies should be repeated before the use of sodium bicarbonate or other bases is deemed useless in the context of resuscitation at birth. It might also be instructive to factor in the use of adrenaline in similar studies and a direct comparison of adrenaline vs. bicarbonate would be of considerable interest.
**REVIEWER’S CONFLICTS OF INTEREST:**

UK NHS Consultant neonatologist. Co-chair of the Neonatal section of ILCOR – unpaid. Chair of the Newborn Life Support subcommittee of the Resuscitation Council (UK) and member of the Executive committee – both unpaid.

No other conflicts.

**Acknowledgements:**

Nil
Citation List

Sodium bicarbonate in neonatal resuscitation
Listing of papers alphabetically by surname of first author
(Includes some papers for background information only)

Adamsons, 1963, p697
Maintenance of arterial pH and provision of glucose as substrate throughout the course of asphyxia in foetal lambs and monkeys prolonged survival and facilitated resuscitation (Dawes, Mott, Shelley & Stafford, 1963; Dawes, Jacobson, Mott, Shelley & Stafford, 1963). The primary object of the present experiments was to see whether it was possible to achieve the same therapeutic effects when infusion of alkali and glucose was begun late in asphyxia, when the circulation had begun to fail. A brief account of these observations has been given elsewhere (Adamsons, Behrman, Dawes, Dawkins, James, Ross & Windle, 1963).
Summary:
1. Mature foetal rhesus monkeys were delivered by Caesarean section under local anaesthesia, and were asphyxiated for 12.5 min.
2. Infusion of alkali (0.7M sodium carbonate or 0.5M Tris) with glucose into the umbilical vein, beginning 6-5 min after the onset of asphyxia, restored the arterial pH, increased the heart rate and raised the blood lactate concentration more rapidly. During asphyxia treated monkeys maintained their blood pressure better and continued to gasp significantly longer than did controls; they also recovered more quickly after artificial ventilation.
3. Much larger volumes of 0.6M sodium bicarbonate were required to restore the arterial pH during asphyxia, and on ventilation the pH rose further as carbon dioxide was eliminated.
4. Injection of sodium carbonate solutions (pH>10) caused acute haemorrhagic necrosis of the liver adjacent to the entry of the umbilical vein, but Tris (at pH 8.85) and sodium bicarbonate solutions did not cause liver damage.
5. It is concluded that treatment with alkali and glucose late in asphyxia, when circulation has begun to fail, maintains the circulation and respiratory efforts, and that for this purpose Tris is to be preferred to sodium carbonate or bicarbonate.
Additional information: In this study monkeys were asphyxiated in transition from placental to pulmonary respiration. Treated monkeys had an infusion of alkali and glucose into the umbilical vein started 6-5 minutes after the cord was tied and lasting 4 minutes. The infusion rate was adjusted to raise the heart rate and to maintain it at 100-120 beats per minute. In the case of 0.7M sodium carbonate the rate required was 1 6 to 1.9 ml/kg/min and for 0.5M Tris it was 3 to 4.4 ml/kg/min. The strength of the glucose solution used varied between 3 and 7.5% - the variation being adjusted to maintain the total quantity of glucose infused to about 0.5 gm/kg. Intubation and ventilation with 100% oxygen was begun at 12.5 minutes. If the heart had stopped beating already or if it did not accelerate within 30-45 seconds, cardiac massage was applied repeatedly for periods of 10-12 sec until it did start to accelerate. When rhythmical respiration was established the catheters and endotracheal tube were removed and the monkey reared in an incubator.

Endpoint: A,E
LOE: 5
Quality: Good
Relevance: Highly relevant
Supportive
Comment: The question we are asking is does the use of bicarbonate improve the immediate outcome in fetuses asphyxiated during the transition from placental to pulmonary respiration if it is given when a combination of ventilation and chest compressions is ineffective. This study does not address the question with absolute precision, in that the administration of bicarbonate in this study occurred after the asphyxial insult but before CPR and was not dependent on failure of ventilation and compressions - but it gets very close. A combination of base with glucose was used.

Adamsons, 1964, p807
Rhesus monkeys delivered by cesarean section were asphyxiated under controlled environmental conditions and then resuscitated by positive pressure ventilation with oxygen. In one half of the monkeys an infusion of Tris and glucose was given into the umbilical vein during resuscitation to restore the arterial pH rapidly to normal values. This reduced the time required to establish spontaneous breathing and increased the initial oxygen uptake. There was a linear relationship between duration of asphyxia and the return of respiratory function: for each minute after the last gasp that resuscitation was deferred, subsequent onset of gasping was delayed about 2 minutes and spontaneous breathing about 4 minutes. Nearly one half of the asphyxiated animals developed respiratory difficulties similar to those seen in human infants suffering from the respiratory distress syndrome.
Summary:
1. Fetal rhesus monkeys were delivered by caesarean section under local anesthesia and were asphyxiated under controlled environmental conditions. They were resuscitated by artificial ventilation with O2 and by cardiac massage, if necessary.
2. Rapid intravenous infusion of alkali (0.5M Tris) with glucose on resuscitation reduced the time required to establish rhythmic breathing, and increased the immediate O2 uptake.
3. The effect of asphyxia for 10, 12.5 or 15 minutes on subsequent resuscitation was analyzed. The mean time from onset of asphyxia until the last gasp was 8.42 minutes. For each minute after the last gasp, the interval from beginning resuscitation until the first gasp was more than 2 minutes, and until the establishment of rhythmic breathing it was more than 4 minutes.

4. Respiratory distress and/or pulmonary edema were observed in 21 of 43 monkeys asphyxiated for 10 to 15 minutes on delivery. The incidence was higher in the monkeys with the lower birth weights. Infusion of alkali and glucose during asphyxia or on resuscitation did not prevent the development of respiratory distress.

Additional information: In this study monkeys were asphyxiated in transition from placental to pulmonary respiration. At a predetermined time one minute or more after the last gasp – i.e. in terminal apnoea – the monkey was intubated and ventilated with oxygen. If the heart did not accelerate within 30 seconds of ventilation then chest compression was begun for 8 to 10 seconds – during which time ventilation was stopped. Infusion of base in glucose – in this case 0.5M Tris (aka THAM) in 3.5% glucose adjusted to pH 8.85 – was given over 2 to 4 minutes during this process.

Endpoint: A
LOE: 5
Quality: Good
Relevance: Highly relevant
Supportive
Comment: These monkeys were definitely in terminal apnoea and treatment was given shortly after commencement of resuscitation. A combination of base with glucose was used.


Endpoint: A
LOE: 5
Quality: Very Good
Relevance: Moderately relevant
Supportive
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. Hypoxia, asphyxia and hypercarbia were allowed to develop for 10 minutes before CPR was initiated. Buffer was given in doses equivalent to those that might be used in newborn resuscitation and the first dose was not given until 8 minutes of CPR had been performed – and one minute after IV adrenaline had been given.

Beveridge, 2006, CD004864
Beveridge CJ, Wilkinson AR. Sodium bicarbonate infusion during resuscitation of infants at birth Cochrane Database of Systematic Reviews 2006 CD004864

LOE: Not listed in tables as merely a repetition of Lokesh 2004
Quality: Fair
Relevance: Repetition without added data or extra analysis
Neutral
Comment: A Cochrane review of the only randomized study in human infants evaluating the role of sodium bicarbonate infusion during resuscitation – see Lokesh 2004. My comments on the Lokesh study were as follows: A small randomized controlled study which concluded that administration of sodium bicarbonate to those asphyxiated babies apparently still needing positive pressure ventilation at five minutes of age does not affect blood pH when measured 6 hours later. Under those guidelines where sodium bicarbonate is used it is only thought to be relevant in those babies who, despite receiving appropriate lung aeration and chest compressions, are unable to produce a heart rate of around 100 beats per minute. Furthermore, the object of the exercise is to produce a heart rate response and to aid resuscitation, not to alter the pH of the baby some hours later.

Bleske, 1992, p525

Endpoint: E
LOE: 5
Quality: Good
Relevance: Moderately relevant
Supportive
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. These observations suggest that if administration of sodium bicarbonate
was contemplated a continuous infusion may be the most desirable mode of administration for the prevention of venous acidosis during CPR.

Bishop, 1976, p506

Endpoint: E
LOE: 5
Quality: Fair
Relevance: Moderately relevant
Opposing
Comment: This study contains both adult human and adult animal data. In the adult dogs ventricular fibrillation was induced by direct-current impulse to the right ventricle by a pacing wire and the ventilator was stopped at the same time. Apnoea and VF continued for 3 minutes before CPR (ventilator + external chest compressions) was started. Sodium bicarbonate, using a 7.5% solution, was given at a dose of 1 mEq/kg over 15 seconds into the superior vena cava. In the adult patients with cardiac arrest a rapid intravenous dose of 44.8 mEq of sodium bicarbonate (7.5%) was given during CPR. At the time of the study guidelines suggested that 1 mEq/kg be given twice “in the initial minutes of resuscitation” followed by 0.5 mEq/kg at ten minute intervals. In the context of neonatal resuscitation the bicarbonate dose of 1 mEq/kg used in this study is in the appropriate range.

Cooper, 1990, p492

Endpoint: E
LOE 5
Quality: Good
Relevance: Minimally relevant
Neutral
Comment: Small study. Strengths include randomized blinded and crossover. Dosage of bicarbonate is in an appropriate range for comparison with neonatal resuscitation use but data from animal experiments would suggest that newborn infants in secondary apnoea would have a pH of less than 7.0 whereas the mean pH in this study was 7.13.

Daniel, 1966, p562

Summary:
Injection of lobeline into the asphyxiated adult and newborn rhesus monkeys during “primary apnoea” caused them to gasp earlier than they otherwise would have done.
Injection of lobeline omikethamide into foetal monkeys in “secondary apnoea” – that is, asphyxiated beyond their last gasp – did not elicit any further gasp and caused the blood pressure to fall more rapidly.
Infusion of an alkali-and glucose solution into foetal monkeys after the last gasp caused a rise in heart rate and blood pressure, and gasping started again.
The results explain why the use of analeptics in asphyxia neonatorum is still sometimes reported on favourably, but show that there are other more reliable and less dangerous methods of resuscitation.
Summary

1. The ability of foetal lambs to survive anoxia has been investigated by recording the foetal blood pressure and heart rate continuously before and after tying the umbilical cords of lambs delivered by Caesarian section under chloralose anaesthesia.

2. Lambs of 83-91 days gestation age maintained their blood pressure above 16 mm Hg and their heart rate above 50 per minute for up to 60 minutes after tying the umbilical cord; if the cord was untied within 40 minutes, the blood pressure and heart rate returned to pre-anoxic levels. Older lambs, 126-146 days gestation age, maintained their blood pressure and heart rate for only 10-15 minutes after tying the cord. Adult sheep rebreathing nitrogen did not survive for more than 7 minutes.

3. The rates of anaerobic glycolysis in foetal lambs were compared by measuring the blood and tissue lactate and carbohydrate levels in unasphyxiated control lambs and in other lambs at various intervals of time after tying the umbilical cord. The initial rates of glycolysis in the tissues of the older lambs were either equal to or greater than those in the younger lambs. There was a correlation between survival time and the initial cardiac carbohydrate concentration in the lambs in each age group.

4. The cardiac carbohydrate concentration has been measured in unasphyxiated new-born rats, rabbits and guinea-pigs of different ages; there was a linear relationship between cardiac carbohydrate concentration and the predicted time of survival in 100% nitrogen.

5. These results have been discussed with reference to previous hypotheses as to the ability of very young animals to survive anoxia longer than adults. It was concluded that the maintenance of circulation is of primary importance in anoxia.

LOE: 5 – Not listed in tables – background only

Quality: Good animal study

Relevance: Background only

Comment: Shows the difference in the ability of fetal hearts to tolerate asphyxia / anoxia as compared to hearts of older mammals. It is for this reason that many animal studies using older mammals and studies in older humans are likely to be less relevant.
Summary:
1. Immature foetal lambs of 74-92 days gestation age were asphyxiated by tying the umbilical cord. When glucose was infused with sufficient base to check the fall in arterial pH, the blood pressure and heart rate fell more slowly than in untreated lambs, the rate of rise of plasma potassium was reduced by 60%, and the blood lactate continued to rise rapidly throughout the period of asphyxia.
2. These effects were not related to changes in haematocrit, haemoglobin concentration and plasma sodium, since the infusion of sodium chloride with glucose was ineffective.
3. The infusion of glucose only or base only was also ineffective.
4. The changes in tissue carbohydrate and lactate concentrations are described.
5. It was concluded that if glycolysis is maintained during asphyxia by checking the fall in arterial pH and providing glucose as substrate, sufficient energy may be available to maintain both the circulation and the integrity of the tissues for longer than in untreated lambs.

Endpoint: A
LOE: 5
Quality: Good animal study
Relevance: Highly relevant
Supportive
Comment: Confirmation of an effect of the infusion of base in fetal animals subjected to severe prolonged asphyxia / anoxia but only if infused together with glucose.

Dawes, 1963, p167
Dawes GS, Jacobson HN, Mott JC, Shelley HJ, Stafford A. The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. J Physiol 1963; 169: 167-84

Summary:
1. Mature foetal lambs of 140-145 days’ gestation age and rhesus monkeys of 139-158 days’ gestation were asphyxiated for a standard time and then resuscitated.
2. When glucose was infused during asphyxia with sufficient sodium carbonate to check the fall in arterial pH, the foetuses gasped for longer than untreated controls, their blood pressure and heart rate fell more slowly, and the blood lactate rose more rapidly.
3. Whereas in untreated monkeys the plasma sodium was unchanged and the haematocrit rose during asphyxia, in treated monkeys there was a large rise in plasma sodium and considerable haemodilution. The plasma potassium rose during the first 5 min asphyxia but was little changed thereafter and was not greatly affected by treatment.
4. On readmitting oxygen treated foetuses recovered more rapidly and possibly more completely than untreated ones.
5. Both during asphyxia and afterwards, the effects of the infusion were greater in the monkeys than in the lambs.

Additional information: Nineteen lambs were delivered, instrumented with the cord intact then the cord was ligated. In the 9 treated lambs sodium carbonate (15g/100ml) in 15% glucose was infused from the onset of asphyxia. The infusion rate was adjusted if necessary at the end of 5 mins asphyxia in an attempt to keep the arterial pH near its original level. The mean infusion rate was 0.23 ml/kg/min (0.21-0.26), i.e. 34.5 mg/kg/min of both glucose and sodium carbonate. After the lamb had ceased to make respiratory efforts the trachea was intubated. Artificial ventilation was administered by a Starling Ideal pump with room air and the infusion, when given, was stopped 5 min later. After regular breathing had been established, the catheters and endotracheal tube were removed and the lamb was rubbed down with a towel and placed on fibre matting on the laboratory floor in front of an electric fire.

In the ten monkeys a similar approach was adopted. Of four monkeys treated one received 14% sod carbonate in 14% glucose at 0.25 ml/kg/min (35 mg/kg/min) and four received 7.5% sod car in 7.5% glucose (0.41 – 0.68 ml/kg/min = 38.1 +/- 1.3 mg/kg/min). One monkey received an infusion of 8.28% sodium chloride in 7.5% glucose at 0.25 ml/kg/min. Infusions were begun at the clamping of the cord and continued throughout.

Endpoint: A
LOE: 5
Quality: Good
Relevance: Highly relevant
Supportive
Comment: A combination of base with glucose was used.

Dawes, 1964, p801

Summary:
1. The brains of mature fetal rhesus monkeys which had been asphyxiated at birth under standardized conditions, with subsequent resuscitation and recovery, were examined microscopically and the degree of permanent damage was assessed. Of the brain stem nuclei, that of the inferior colliculus proved the best guide.
2. Administration of alkali and glucose during asphyxia reduced the incidence and the extent of brain damage. There was a good correlation between physiologic observations and pH changes in the blood during asphyxia and resuscitation and the histologic evidence of permanent brain damage.
Endpoint: E
LOE: 5
Quality: Good animal study
Relevance: Moderately relevant
Supportive
Comment: The monkeys in question were those whose fate is described in the papers already listed - Adamsons 1963, 679 and Dawes 1963, 167. Though this paper produces some further evidence to support the use of base with glucose in resuscitation at birth it must be admitted that histology is not a very sensitive way of assessing brain damage.

Dybvik, 1995, p89

Endpoint: B,D,E
LOE: 5
Quality: Good
Relevance: Moderately relevant
Neutral
Comment: Randomized study of bicarbonate versus saline in asystolic out of hospital adult cardiac arrest patients of whom one third in both groups were admitted to the ICU. Logistic modelling showed no improvement in outcome with buffer therapy. This is the only human randomized study addressing this specific question. However, adult hearts are known to be considerably less tolerant of anoxia/asphyxia than those of babies in transition from placental to pulmonary respiration.

Federiuk, 1991, p1173

Endpoint: A
LOE: 5
Quality: Fair
Relevance: Moderately relevant
Neutral
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. They were allowed to become hypoxic, ischaemic and hypercarbic. The use of sodium bicarbonate did not improve resuscitation from prolonged cardiac arrest.

Guerci, 1986, p75

Endpoint: A
LOE: 5
Quality: Fair
Relevance: Moderately relevant
Neutral
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. The data do not suggest a primary role for sodium bicarbonate in resuscitation following ventricular fibrillation in adult dogs. The relevance to the neonate at birth who presents with hypoxia, ischemia, bradycardia and a mixed metabolic and respiratory acidosis is unclear.

Kette, 1990, p1660

Endpoint: E
LOE: 5
Quality: Fair
Relevance: Moderately relevant
Neutral
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. Administration of buffer agents, without glucose, directly into the heart
increased systemic venous and sinus venosus pH but had no apparent effect on intramyocardial pH. Given that one of the theoretical reasons for giving buffers in this situation is to improve intramyocardial pH this finding is important.

Kette, 1991, p2121


Endpoint: E
LOE: 5
Quality: Good
Relevance: Moderately relevant

Opposing
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. Sodium bicarbonate solution in the absence of vasopressor agents may adversely affect cardiac resuscitation by reducing the coronary perfusion pressure below critical thresholds.

Laptook, 1985, p815


Additional information: Once instrumented and ventilated the piglets were rendered hypoxic by decreasing inspired oxygen to 13%. Hypoxemia was continued until arterial pH was less than 7.25 at which point the second BBF determination was performed. After this was completed the piglets were randomised to receive either an infusion of 0.5M sodium bicarbonate (2 mEq/kg) over 3 minutes or an equivalent volume of normal saline. PaCO₂ was maintained constant (at 35-40 mm Hg – 4.6-5.3 kPa) by ventilator adjustment.

Endpoint: E
LOE: 5
Quality: Good
Relevance: Moderately relevant
Neutral

Comment: These piglets were all at least 6 days old and thus had already completed the transition from placental to pulmonary respiration by the time of the experiment. Their hearts would also presumably have had considerably less glycogen stores than at birth. They were also rendered hypoxic but not hypercarbic. Correction of metabolic acidosis in these pigs does not appear to alter brain blood flow or oxygen delivery

Leong, 2001, p309


Endpoint: A
LOE: 5
Quality: Good
Relevance: Moderately relevant
Supportive

Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. These data suggest that following prolonged arrest, bicarbonate therapy and a period of perfusion prior to defibrillation may increase survival. VF is not the issue in neonatal resuscitation. However longer-term outcome and in particular CNS outcome is not provided. There is biochemical, histological and clinical evidence that the cumulative energy dose delivered to the myocardium during defibrillation attempts is associated with myocardial damage, which decreases the likelihood of successful resuscitation. This is not a concern to the neonatal population.

Levy, 1998, p457


This was an evidence based review that addressed the following question: what evidence supports the use of sodium bicarbonate in the therapy of acidosis associated with cardiac arrest during CPR Human studies (n=21)

Only one study, Dybvik T et al, was prospective. As noted above, this study did not demonstrate a beneficial effect of buffer on ROSC or outcome after out of hospital cardiac arrest. (It was suggested that the study was underpowered and that it would take 4200 patients to show a difference.) None of the retrospective studies showed any benefit, eight studies suggested a deleterious effect and 12 studies showed no difference. With regard to outcome 4 showed improved survival and 7 showed no difference. Regarding myocardial performance, none showed benefit, 12 were deleterious and 2 showed no difference. The author’s conclusions included the following:
1) No human study has demonstrated a beneficial impact on survival
2) Several adult human studies (level 3 and 4) have demonstrated deleterious effects on physiologic end points from the administration of bicarbonate during CPR
3) Several animal studies have demonstrated impaired function in response to bicarbonate administration during CPR
4) Several animal studies (n=4) have demonstrated survival benefit from the administration of bicarbonate during CPR

LOE: 5
Quality: Good review of available literature aimed at adult events
Relevance: Minimally relevant
Neutral
Comment: All human studies evaluated concerned events in adults and all animal studies evaluated also used adult animals. Neonatal animal studies (e.g. Adamsons 1963 etc) were not mentioned.

Lokesh, 2004, p219

Endpoint: C,D,E
LOE 1
Quality: Fair
Relevance: Moderately relevant
Neutral
Comment: Small randomized controlled study which concluded that administration of sodium bicarbonate to those asphyxiated babies apparently still needing positive pressure ventilation at five minutes of age does not improve survival nor does it affect blood pH measured 6 hours later. Under those guidelines where sodium bicarbonate is used it is only thought to be relevant in those babies who, despite receiving appropriate lung aeration and chest compressions, are unable to produce a heart rate of around 100 beats per minute. The pH of the baby some hours later is not a relevant outcome. Same patient population as Murki 2004

Lou, 1978, p239

Endpoint: E
LOE 5
Quality: Poor.
Relevance: Minimally relevant
Neutral
Comment: These babies seem to have received bicarbonate infusion in response to respiratory symptoms – presumably using something similar to the “Usher Regimen” (see description in comments on Simmons 1974 below). All were preterm (29 – 34 wks), had been only mildly acidotic at birth (pH 7·11 to 7·24), and all but two (both 29 weeks gestation) had Apgar scores above 6 at five minutes. The clinical implication of these observations is unclear but it is possible that the reduction in CBF may be secondary to bicarbonate induced cerebral vasoconstriction.

Murki, 2004, p696

Endpoint: E
LOE: 1
Quality: Fair
Relevance: Moderately relevant
Neutral
Comment: Small randomized study which shows that administration of sodium bicarbonate to those asphyxiated babies apparently still needing positive pressure ventilation at five minutes of age does not affect blood pH when measured 6 hours later. However, sodium bicarbonate is only suggested as being necessary in those babies suffering from asphyxia who are unable to produce a heart rate of around 100 beats per minute despite appropriate lung aeration and chest compressions. Furthermore, the object of the exercise is to produce a heart rate response and to aid resuscitation, not to alter the pH of the baby some hours later. Same patient population as Lokesh 2004

Neumar,1995, p249

Endpoint: E
LOE: 5
Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Asphyxia was produced by disconnecting the ventilator and clamping the inhalation tubing – apart from the fact that the asphyxia occurs in relation to pulmonary respiration rather than placental, this method of asphyxia better represents the asphyxia, hypercarbia and consequent ischaemia and metabolic acidosis found in the newborn at birth. Interestingly, bicarbonate did not seem to reduce coronary perfusion pressure in this experiment (cf Kette, 1991).

Preziosi, 1993, p1901

Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. Use of adrenaline infusion maintained blood pressure and presumably also the arterial pH. Once again a significant respiratory acidosis was avoided by maintaining arterial PCO₂ at normal levels and the arterial pH values did not fall below 7.18; a very modest variation from the normal in the context of birth asphyxia. In the context of neonatal resuscitation of the severity which might involve the use of drugs we would expect a pH of 6·9 or less and a base deficit of -20 or so together with profound hypoxia. Presumably the differences in brain pH would have been greater had the pH been allowed to fall further before rescue but really this study really tells us little of relevance to the neonatal resuscitation scenario.

Rubertsson, 1993, p1051

Comment: These were adult animals, not in transition from placental to pulmonary respiration and were more than one week old. Thus they would presumably have hearts with considerably less glycogen in them than at birth. Use of sodium bicarbonate alone in this study appeared to increase rather than decrease blood pressure; and to increase it slightly more so than other buffers – however, when sodium bicarbonate was combined with adrenaline systemic blood pressure was lower than other combinations. As ventilation was continued there was no opportunity for hypercarbia to develop.

Sessler, 1987, p817
Simmons, 1974, p6


Endpoint: E
LOE: 5
Quality: Poor
Relevance: Minimally relevant

**Opposing Comment:** This paper compares and contrasts the incidence of intracranial haemorrhage (diagnosed at autopsy) and hypernatraemia occurring amongst admissions to a neonatal unit in two time periods each of one year but separated by 3 years. In the second time period the use of sodium bicarbonate was restricted compared to the first. The mortality rate was almost halved in the second time period. In my view the more likely explanation for this finding is a doubling of the admission rate in the second period from 238 to 468 per year. A change in admission rate of this magnitude suggests that the sodium bicarbonate policy was not the only one to change over this time. Furthermore, limitation of use of bicarbonate would almost certainly lead to use in only the most severe cases which gives rise to the equally tenable explanation that the IVH was the cause of the deterioration for which the bicarbonate was given rather than a result of its use. There is also an unfortunate misprint in the abstract which suggests that the authors warn against a daily intake of sodium greater than 8 mg/kg when in fact they mean 8 mmol/kg – or 184 mg/kg (the atomic weight of sodium is 23). Case control studies using retrospective controls are frequently misleading and are unlikely to be published in the modern era. However, there is little doubt that excessive administration of sodium, whether as bicarbonate or another salt, will lead to hypernatremia.

The “Usher regimen” for management of RDS referred to in this paper involved the infusion of a solution of 10% dextrose in water to which was added a variable amount of sodium bicarbonate adjusted according to the blood pH of the baby using the following algorithm taken from Usher R. The respiratory distress syndrome of prematurity: clinical and therapeutic aspects. *Ped Clin North America* 1961; 8: 525-38.

<table>
<thead>
<tr>
<th>Venous pH</th>
<th>Arterial of capillary pH</th>
<th>Sodium bicarbonate concentration (mEq/100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 7.20</td>
<td>Over 7.30</td>
<td>5</td>
</tr>
<tr>
<td>7.10 – 7.20</td>
<td>7.20 – 7.30</td>
<td>10</td>
</tr>
<tr>
<td>7.00 – 7.10</td>
<td>7.10 – 7.20</td>
<td>15</td>
</tr>
<tr>
<td>Under 7.00</td>
<td>Under 7.10</td>
<td>25</td>
</tr>
</tbody>
</table>

The resulting solution was given intravenously at a rate of 65 ml/kg per day – i.e. providing a sodium load of 3.25 to 16.25 mEq/kg per day. (For sodium 1 mEq = 1 mmol). Where bicarbonate is recommended in newborn resuscitation a single dose of 1-2 mmol/kg is suggested.

Incidentally, Robert Usher was clearly a “hands-on” practitioner; the extent to which this is true is revealed by the fact that of the 78 premature infants with RDS born over a 2 year period who were eligible for entry into his randomised study only 8 were not entered, "because the author was unable to examine them within 3 hours of their delivery".

Stafford, 1960, p153


**Summary:**
1. The times to last breath of new-born rats in nitrogen increased with decreasing environmental temperatures. Heart carbohydrate was depleted more rapidly at higher temperatures.
2. During exposure of new-born rats to nitrogen, the heart carbohydrate was almost depleted, the liver carbohydrate was depleted or reduced, and the skin, muscle and lung carbohydrate concentrations were only slightly decreased. Increase in blood glucose was related to the concentration of carbohydrate in the liver. Loss in liver and heart carbohydrate during exposure of new-born rats to nitrogen accounted for 72% of the lactic acid production, but during the first day of life while the liver carbohydrate was rapidly falling, the time to last breath in nitrogen decreased only slightly.
3. Heart carbohydrate and survival time in nitrogen decreased steadily between 0 and 16 days of age; liver carbohydrate fell from a mean of 58 mg/g to a minimum (<10 mg/g) during the first 24 hr of life and increased gradually to adult levels (33 mg/g) at about 16 days of age.
4. During depletion of liver and heart carbohydrate by fasting, survival time decreased in the same proportion as heart carbohydrate. When the tissue carbohydrate was reduced by exposure to nitrogen, heart carbohydrate and survival time in rats re-exposed to nitrogen recovered in the same proportion.
5. Insulin (1-2 units/g) reduced the blood glucose of new-born rats to less than 20 mg/100 ml and reduced the mean time to last breath in nitrogen to 14.2 min; initial heart carbohydrate and the time for which heart beats persisted in nitrogen were only slightly reduced by insulin.
6. The survival time of new-born rats in nitrogen were prolonged by intraperitoneal injection of glucose only under the following conditions: (a) in litters in which untreated rats died with a very low blood glucose or (b) in rats whose carbohydrate levels were depleted by previous exposure to nitrogen. The survival times of 8- and 18-day-old rats were slightly but significantly increased by glucose injection 10 min before exposure to nitrogen.

LOE: 5 – Not listed in tables – background only
Quality: Good
Relevance: Background

Comment: Further detail concerning the importance of cardiac glycogen levels in the maintenance of cardiac function during asphyxia in newborn mammals.

von-Planta, 1988, p594

Additional information: The pigs in this study were 3 months old. They were intubated and ventilated with oxygen (21% or 100%) throughout. VF was induced electrically, ventilation was continued but chest compressions (synchronised 5 to 1 with ventilation) were only started after 5 minutes.

Endpoint: E
LOE: 5
Quality: Good
Relevance: Moderately relevant
Neutral

Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. Tris (aka Tromethamine or THAM) appeared to decrease coronary perfusion pressure in this experiment but this does not appear to have been the case with sodium bicarbonate. However, as ventilation was continued, there was no opportunity for hypercarbia to develop.

Vukmir, 1995, p515

Additional information: The dogs weighed between 10 and 17 kg. VF was induced electrically and ventilation was discontinued for 5 or 15 minutes following induction of VF.

Endpoint: A,B
LOE: 5
Quality: Good
Relevance: Moderately relevant
Supportive

Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. During the time arrest was maintained hypercarbia could develop. Given that resuscitability was unaffected (5 mins) or improved (10 mins) in this experiment, presumably there was no significant effect of the sodium bicarbonate dose on coronary perfusion pressure (cf Kette, 1991). Empirical administration of bicarbonate appears to have improved the survival rate and neurologic outcome in this adult canine model of cardiac arrest. These observations support the current recommendation of sodium bicarbonate administration following prolonged resuscitation in the face of adequate ventilation.

Wheeler, 1979, p517

Endpoint: E
LOE: 5
Quality: Good
Relevance: Highly relevant
Supportive - indirectly

Comment: Lambs in transition from placental to pulmonary respiration were studied with asphyxia being induced while relying on placental respiration. Resuscitation attempts were designed to encourage pulmonary respiration. Full correction of metabolic acidosis with intravenous 4-2% sodium bicarbonate in 5% dextrose – dosage given 6.4 mmol/kg (12.4 ml/kg solution) +/- 0.8 mmol/kg (+/- 1.6 ml/kg) - was not associated with intraventricular haemorrhage.

Wiklund, 1990, p430
Additional information: The pigs weighed 18 – 26 kg. VF was induced electrically while ventilated and manual external chest compressions with simultaneous ventilation were begun immediately.

Endpoint: A
LOE: 5
Quality: Good
Relevance: Moderately relevant

Comment: These were adult animals, not in transition from placental to pulmonary respiration and thus they would presumably have hearts with considerably less glycogen in them than at birth. Cardiac arrest was induced by ventricular fibrillation and was not secondary to respiratory arrest as would be the cause at birth. Sodium bicarbonate infusion was associated with higher PCO$_2$. 