**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| Edison Paiva | Date Submitted for final review: 26 November 2009 |

**Clinical question.**

In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of buffering agents alone or combination with other drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (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 W34, W100A, W100B

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? None

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


**Embase:** The search strategy ('sudden death'/exp OR 'resuscitation'/exp OR 'heart arrest'/exp OR 'fibrillation heart'/exp) AND ('bicarbonate'/exp OR 'buffer'/exp OR 'tromethamine'/exp OR 'carbicarb'/exp OR 'tham'/exp) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [article]/lim AND [embase]/lim AND [medline]/lim produced 24 references.

**AHA Endnote Master Library:** The search strategy “cardiac arrest” and bicarbonate or buffer produced 236 references.

**Lilacs:** The search terms used and the respective references produced were: arrest and bicarbonate – 16; arrest and buffer – 2; arrest and tromethamine – 1; ventricular and fibrillation and bicarbonate – 4; sudden and death and bicarbonate – 1; resuscitation and bicarbonate – 22; resuscitation and buffer – 1. The other combinations of the terms arrest, “ventricular fibrillation”, “sudden death” or resuscitation with buffer, tromethamine, tham, borate, tribonate or carbicarb produced no references. No exclusion criteria were used.

**Cochrane database for systematic reviews.** Combination of the terms “cardiac arrest”, “ventricular fibrillation”, “sudden death” or resuscitation with bicarbonate, buffer, tromethamine, tham, borate, tribonate or carbicarb produced only one systematic review about infusion of sodium bicarbonate in infants receiving resuscitation in the delivery room at birth.

Hand searching of papers selected by other strategies was done, but no additional references were found.

**State inclusion and exclusion criteria**

Inclusion criteria: human studies in all languages. One study that mixes results of a dog experiment with observations in 6 VF patients was included (Bishop, 1976)

Exclusion criteria: not cardiac arrest studies, neonatal resuscitation, studies were bicarbonate was measured but not administrated, reviews and editorials. One article in Japanese was also excluded.

**Number of articles/sources meeting criteria for further review:** Eighteen
# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>B = Survival of event</td>
<td>D = Intact neurological survival</td>
<td>E = Other endpoint</td>
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</table>

### Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tbody>
<tr>
<td>D = Intact neurological survival</td>
<td>E = Other endpoint</td>
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</table>

### Evidence Opposing Clinical Question

<table>
<thead>
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<th>Level of evidence</th>
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<th>Fair</th>
<th>Poor</th>
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<tbody>
<tr>
<td>B = Survival of event</td>
<td>C = Survival to hospital discharge</td>
<td>Skovron, 1985 E</td>
<td>Weil, 1985 E</td>
</tr>
<tr>
<td>D = Intact neurological survival</td>
<td>E = Other endpoint</td>
<td>Weil, 1986 E</td>
<td></td>
</tr>
</tbody>
</table>

### Level of evidence

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

*Italics = Animal studies*
Sodium bicarbonate (SB) was introduced into the first Standards for Cardiopulmonary Resuscitation and Emergency Cardiac Care of the AHA in 1974 because metabolic acidosis, developing during cardiac arrest, was believed to be detrimental to outcome. Since 1986 the administration of SB was discouraged not only because of lack of sufficient evidence for a beneficial effect, but mainly because of concerns about hyperosmolality and hypernatremia.

Recommendations about avoiding sodium bicarbonate during cardiac arrest are mostly based on fair and poor cohort studies (Roberts, 1990; Suljaga-Pechtel, 1984; Skovron, 1985; Van Walraven, 1998) and case series (Bishop, 1976; Weil, 1985; Weil, 1986). Cohort studies show a negative relation between survival and bicarbonate use, which was usually indicated in longer resuscitations, if initial measurements were not effective. Probably the worse outcome associated with bicarbonate reflects the underlying condition of the patients rather than the deleterious effects of the drug, and sodium bicarbonate administration is just an “epiphenomenon” of the prolonged arrest.

Hyperosmolality and hypernatremia have been extensively shown as adverse effects secondary to bicarbonate infusion, but in some studies this relation has not been proved (Aufderheide, 1992; Dybvik, 1995), and probably high glucose levels after resuscitation, specially in old studies where glucose infusion was common (Martinez, 1979; Gueugniaud, 1989), may have contributed to hyperosmolality.

On the other side, evidence supporting bicarbonate use in cardiac arrest is also based only on 2 cohort studies (Bar-Joseph, 2005; Gueugniaud, 1989), one retrospective control study (Weaver, 1990) and one case series of 16 patients (Martinez, 1979). On Bar-Joseph’s study, bicarbonate impact on outcome was a secondary analysis based on the frequency of bicarbonate use by 16 different sites involved on an epinephrine dose trial. In Gueugniaud’s cohort, only 50 out-of-hospital successfully resuscitated patients where analyzed. Survivors had normal or high pH, and received an average dose of 1.6 mEq/Kg of bicarbonate. Weaver compared survival during a randomized controlled trial of epinephrine vs lidocaine to an historical control. There were differences between groups in time delay for the first shock and proportion of bystander CPR, which might have biased conclusions.

There are only 2 randomized controlled trials, one comparing tribonate to saline (Dybvik, 1995) and the other bicarbonate to saline (Vukmir, 2006), both showing no influence of buffer on outcome. In Dybvik’s study, response time was short (5.8 min) and only moderate metabolic acidosis was detected in both groups, making bicarbonate use possibly not necessary. Although Vukmir’s study was published in 2006, the database is from a much older period (1994 to 1998) and the randomization method is not specified. There is also some controversy about results, because wrong proportions were compared.

Four other low level studies have failed to show any impact of buffer use on cardiac arrest outcome. One retrospective cohort of 273 successfully resuscitated cardiac arrest patients who had arterial blood gases and electrolytes measured (Aufderheide, 1992), one retrospective cohort of 748 PEA arrests (Herlitz, 1995), one retrospective in-hospital study with only 254 patients with historical control (Smith, 1965), and 1 case series with 14 ischemic arrests designed to evaluate influence or sodium bicarbonate on arterial blood gases (Fillmore, 1970).

Other non-CO₂ generating buffers as THAM and carbicarb have never been studied in humans. Table 1 presents the results of controlled trials and cohort studies evaluating the use of buffers during cardiopulmonary resuscitation in humans.

In summary, the low quality of the studies make it very hard to take a definitive conclusion about use of buffers during cardiopulmonary resuscitation, and only a large prospective clinical trial may provide a definitive answer.
Table 1. Human studies evaluating buffers in cardiopulmonary resuscitation.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>LOE Quality</th>
<th>N</th>
<th>Characteristics</th>
<th>Buffer</th>
<th>Dose</th>
<th>Outcome (%)</th>
<th>RRR/OR 95% CI</th>
<th>Hospital discharge (%)</th>
<th>RRR/OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Buffer</td>
<td></td>
<td>Control</td>
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<tr>
<td>Tribonate – neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dybvik, 1995</td>
<td>1 Fair</td>
<td>502</td>
<td>Prospective RCT, double blinded, OOH, VF after 1st unsuccessful shock and asystole</td>
<td>Tribonate vs saline</td>
<td>250 mL</td>
<td>HA 35.5</td>
<td>HA 35.8</td>
<td>RRR 0.0</td>
<td>(-0.14-0.12)</td>
</tr>
<tr>
<td>Herlitz, 1995</td>
<td>2 Poor</td>
<td>748</td>
<td>Retrospective Cohort, OOH PEA</td>
<td>Tribonate vs No tribonate</td>
<td>225 mL</td>
<td>HA 15.9</td>
<td>HA 11.6</td>
<td>OR 1.4</td>
<td>(0.91-2.27)</td>
</tr>
<tr>
<td>Bar-Joseph, 2005</td>
<td>2 Poor</td>
<td>2122</td>
<td>Retrospective Cohort, OOH cardiac arrest</td>
<td>High vs low SB users</td>
<td>Not applicable</td>
<td>RO3C 33.5</td>
<td>RO3C 26.7</td>
<td>OR 1.36</td>
<td>(1.08-1.70)</td>
</tr>
<tr>
<td>Weaver, 1990</td>
<td>3 Poor</td>
<td>199</td>
<td>Prospective, pseudo-randomized, not-blinded, with historical control, OOH VF after 1st unsuccessful shock</td>
<td>SB</td>
<td>180 mEq</td>
<td>HA 64.3</td>
<td>HA 50.8</td>
<td>RRR 0.27</td>
<td>(0.09-0.42)</td>
</tr>
<tr>
<td>Vukmir, 2006</td>
<td>1 Fair</td>
<td>792</td>
<td>Prospective RCT, double blinded, OOH resistant VF</td>
<td>SB vs saline</td>
<td>1 mEq/Kg</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.8</td>
</tr>
<tr>
<td>Smith, 1965</td>
<td>3 Poor</td>
<td>254</td>
<td>Retrospective, In-hospital cardiac arrest with historical control</td>
<td>High dose SB vs “lower” dose</td>
<td>89-200 mEq vs not informed</td>
<td>24 h Survival 33.3</td>
<td>24 h Survival 29.7</td>
<td>RRR -0.05</td>
<td>(-0.22-0.12)</td>
</tr>
<tr>
<td>Skovron, 1985</td>
<td>2 Fair</td>
<td>208</td>
<td>Prospective Cohort, In-hospital cardiac arrest</td>
<td>SB vs No SB</td>
<td>NA</td>
<td>6 m Survival 7.1</td>
<td>6 m Survival 32.0</td>
<td>OR 0.16</td>
<td>(0.06-0.45)</td>
</tr>
<tr>
<td>Delooz, 1989</td>
<td>2 Fair</td>
<td>2508</td>
<td>Retrospective Cohort, OOH cardiac arrest</td>
<td>High vs low SB users</td>
<td>&gt;1 mEq/Kg vs less</td>
<td>14 d Survival 10.8</td>
<td>14 d Survival 21.2</td>
<td>OR 0.45</td>
<td>(0.36-0.56)</td>
</tr>
<tr>
<td>Roberts, 1990</td>
<td>2 Fair</td>
<td>310</td>
<td>Retrospective cohort, In-hospital cardiac arrest</td>
<td>SB</td>
<td>NA</td>
<td>ROSC 30.0</td>
<td>ROSC 63.9</td>
<td>OR 0.23</td>
<td>(0.13-0.40)</td>
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<tr>
<td>Van Walraven, 1998</td>
<td>2 Fair</td>
<td>773</td>
<td>Prospective Cohort, In-hospital cardiac arrest</td>
<td>SB</td>
<td>NA</td>
<td>1 h Survival 19.0</td>
<td>1 h Survival 41.5</td>
<td>OR 0.31</td>
<td>(0.21-0.44)</td>
</tr>
</tbody>
</table>

LOE indicates level of evidence; RRR, relative risk reduction; OR, odds ratio; CI, confidence interval; RCT, randomized controlled trial; OOH, out-of-hospital; VF, ventricular fibrillation; HA, hospital admission; PEA, pulseless electrical activity; SB, sodium bicarbonate; NA, not applicable; and ROSC, return of spontaneous circulation.

Acknowledgements:
Citation List

Level 2. Fair. Neutral.
Comments: Review of 273 OOH cardiac arrests successfully resuscitated who had arterial blood gases and electrolytes measured. Fifty-eight (21.2%) patients had short CPR times (7.4 ± 5.5 min) and did not receive bicarbonate; 215 (78.8%) had longer CPR times (23.3 ± 13.5 min) and received bicarbonate. No differences in survival to hospital survival were found. Bicarbonate use was not associated with hyperosmolality or hypernatremia. Paper provides data that allows an analysis of survival at hospital discharge for patients initially in VF (121 patients). Bicarbonate use was associated to lower discharge survival (56.2% vs 75.0%; OR 2.34 95% CI 1.05-5.21).

Level 2. Poor. Supporting.
Comments: Secondary analysis of a RCT designed to test different doses of epinephrine. Sodium bicarbonate use was not randomized and was not the main objective of the study. Analysis of outcome according to buffers usage by the 16 participating EMS systems found a positive correlation between early and more frequent use of bicarbonate and significantly better short- and long-term outcome.

Level 4. Poor. Opposing.
Comments: The study mixes results of a dog experiment with observations in 6 VF patients that had arterial pH, pCO₂ and osmolality measured before and after 2 minutes of quick infusion of 44.8 mEq of SB. pH increased from 7.23 to 7.48, pCO₂ from 24.5 to 38.8 mmHg, and osmolality from 308 to 343 mOsm/kg. Four minutes after infusion, osmolality was almost back to previous measure, and the same happened to pH and pCO₂ after 2 minutes more. The study shows transitory effects on pH, pCO₂ and osmolality, but does not allow conclusions on survival.

Level 2. Fair. Opposing.
Comments: Retrospective analysis of out-of-hospital cardiac arrest with arrest-CPR time ≤ 5 min and total CPR time < 41 min. A negative correlation was done between infusion of more than 1mEq/Kg of sodium bicarbonate and survival with regaining of consciousness at 14 days.

Level 1. Fair. Neutral.
Comments: Although unpowered, this is the only prospective randomized controlled trial designed to compare buffer and placebo. Comparison is between tribonate and saline in asystole and ventricular fibrillation resistant do 1st shock. No effect on hospital admission or hospital discharge was shown, but also no adverse effects were induced. Response time was short (5.8 min) and consequently only moderate metabolic acidosis was detected in both groups upon hospital admission.

The present study documents by serial blood gas measurements that temporary support of the arrested circulation is more likely to be effective when prompt ventilation and endotracheal intubation are performed. Intubation is associated with lower arterial PCO$_2$ and higher oxyhemoglobin saturation. When arterial PCO$_2$ is near normal, bicarbonate is more effective in normalizing blood pH. Even when normal blood pH is achieved, extremely high blood lactate values may be present. Unsatisfactory blood gas values occurring in intubated, vigorously breathed patients probably reflect impairment of gas exchange due to fluid-filled lungs. Serial blood gas studies have proved useful in understanding and testing the physiologic consequences of cardiopulmonary arrest.


Comments: Case series of 14 patients with ischemic heart disease cardiac arrests. Prospective study designed to evaluate influence or sodium bicarbonate on arterial blood gases. Normal pH was more easily maintained after successful intubation and ventilation.


Level 2. Poor. Supporting.

Comments: Prospective cohort of 50 OOH cardiac arrests successfully resuscitated and admitted to the Intensive Care Unit. All patients received 5% dextrose infusion, epinephrine and bicarbonate. Survivors had normal (4/9 – 44.4%) or high pH (5/7 – 71.4%) when admitted. In those with pH lower than normal the survival rate was 8.8% (3/34). Survivors received an average dose of 1.6 mEq/Kg of bicarbonate.


Level 2. Poor. Neutral.

Comments: Retrospective cohort limited to out-of-hospital PEA. Twenty-eight percent of patients received tribonate based on physician’s decision. No relation between tribonate and outcome was detected. More patients were given medication during daytime what makes suspect of possible bias.


Level 4. Poor. Supporting.

Comment: Sixteen randomly selected ICU patients (postoperative and acutely ill) prospectively studied during and after CPR. Sodium bicarbonate was administered at 1 mEq/kg initially (up 2 times) followed by 0.5 mmol/kg every 10 minutes during CPR (mean doses 280 mEq). All patients were successfully resuscitated (ROSC) and 3 were discharged alive. pH was maintained at means of 7.26-7.34 following each dose of sodium bicarbonate, despite some respiratory acidosis (mean pCO$_2$ values 49-56 mmHg). Hiperosmolality was present in 90% before bicarbonate infusion. After bicarbonate, osmolality increased from 337.6 to 361.7 mOsm/Kg and sodium from 144.3 to 156.3 mEq/L. Thirty minutes after successful resuscitation, osmolality and sodium were still high, 161.0 mEq/L and 364.5 mOsm/kg, respectively. Glucose level also increased from 339.5 to 442.8 after bicarbonate, what might have helped to increase osmolality.


Level 2. Fair. Opposing.

Comments: In-hospital retrospective cohort with 310 cardiac arrest victims. Only 4.2 percent (ten of 238) of those who received sodium bicarbonate eventually survived. Of those who did not receive sodium bicarbonate, 27.8 % (20 of 72) were discharged. Authors state that poor outcome of patients receiving sodium bicarbonate probably reflects severe prearrest and intra-arrest metabolic acidosis. Poor outcome in all of these
retrospective analyses is secondary to prolonged arrest/CPR, and sodium bicarbonate administration is just an “epiphenomenon” of the prolonged arrest.

Level 2. Fair. Opposing.
Comments: Prospective in-hospital arrest. Use of bicarbonate negatively associated with survival in multivariate analysis. Authors state that it’s possible that the worse outcome associated with bicarbonate reflects the underlying condition of the patients rather than the deleterious effects of the drug.

Comments: Retrospective in-hospital study with historical control. Experimental group differed from control in the use of defibrillation and higher doses of bicarbonate (89-200 mEq); the dose used initially is not informed. Differences were not statistically significant. In 3 patients, cessation of arrest coincided with correction of metabolic acidosis and in one occasion attempts at defibrillation were successful only after the administration of bicarbonate.

Level 2. Poor. Neutral.
Comments: Study performed in one hospital with a specific medical protocol that included bicarbonate administration to asystole, PEA and VF resistant to initial defibrillation. Patients whose first pH during resuscitation was less than 7.2 were significantly less likely to be resuscitated, and among these patients, those whose pH had not risen by the time of the second blood gas were also less likely to survive. Survival less likely when bicarbonate was given (44.4% vs 76.9%). The worse outcome probably reflects occurrence and severity of the acidosis prior to cardiac arrest, what is known to have an ominous prognosis.

Level 2. Fair. Opposing.
Comments: Secondary analysis of a RCT designed to evaluate the impact of an active compression-decompression device on survival to cardiac arrest. Association of epinephrine and unsuccessful resuscitation may be confounded by the increased probability of epinephrine utilization when patients are not revived, particularly after the 1st shock for ventricular fibrillation. Patients receiving the ACLS medications may also have clinical factors that result in poorer outcomes independent of the drugs.

Level 1. Fair. Neutral.
Comments: Randomization method is not specified. The authors state that bicarbonate improved outcome in prolonged (>15 minute) arrest with a 2-fold increase in survival (32.8% vs 15.4%; P = 0.007), but wrong proportions were compared, as discussed by Pallin DJ [Am J Emerg Med. 2006;24(5):645-6]. When correct statistics is applied, differences are not significant.

Level 3. Poor. Supporting.
Comments: Prospective, non-randomized, not blinded OOH ventricular fibrillation, comparing epinephrine to...
lidocaine after 1st unsuccessful shock. Bicarbonate was not used and results were compared to historical control, when bicarbonate was given by continuous infusion after the 1st unsuccessful shock. Proportion of patients who received bystander initiated cardiopulmonary resuscitation tended to be higher during the later period than during the early period, that is, 41% versus 33%, which might bias toward higher survival rates for patients treated with epinephrine or lidocaine, but the time delay between shocks 1 and 2 was significantly longer in patients treated with epinephrine and lidocaine (5.0±2.0 vs. 4.1±2.7 minutes, p=0.004). Hospital admission was higher in the historical group that received bicarbonate (RRR= 0.27 95% CI 0.09-0.42.

Comments: Retrospective case series of 105 in-hospital and out-of-hospital cardiac arrests with ROSC after resuscitation attempt. All patients received bicarbonate 1 mEq/Kg followed by 0.5 mEq/Kg every 5 minutes. There was a sharp decrease in discharge survival when pH exceeded 7.55, but also when pH was low. Whole blood bicarbonate was significantly higher in fatalities than in survivors. Hyper and hypoosmolality also prognosticated a bad outcome.

Comments: Prospective case series of 16 ICU cardiac arrests with arterial and central venous blood gases analysis during and after resuscitation attempt. Large differences in pH (7.41 vs 7.15) and pCO₂ (32 vs 74 mmHg) were detected, and mixed venous blood was considered a better representation of resuscitation than arterial. Bicarbonate may have worsen venous acidosis, but the author comments on animal studies showing a progressive venoarterial gradient of pH and pCO₂ between mixed venous and arterial blood, in the absence of sodium bicarbonate therapy.