

**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care****Worksheet author(s)**

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**Date Submitted for review:** 12/23/2009**Clinical question.**

Does the treatment of electrolytes derangements improve patient oriented outcomes (i.e survival to hospital discharge or neurological status) in patients with cardiac arrest?

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Therapy

**State if this is a proposed new topic or revision of existing worksheet:** New topic, but encompasses prior worksheet on magnesium therapy

ALS-SC-076A

**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).**

The Cochrane Database of Systematic Reviews was searched with the following terms:

((('cardiac arrest' or 'heart arrest' or cardiopulmonary resuscitation) and (hypokalemia or hyperkalemia or 'hyponatremia' or 'hypernatremia' or 'magnesium' or 'potassium' or 'calcium' or 'hypocalcemia' or 'hypercalcemia') and (outcome or 'mortality')).mp. [mp=title, abstract, full text, keywords, caption text])

EMBASE and MEDLINE were searched with the following terms:

('cardiac arrest'/exp OR 'heart arrest'/exp OR 'cardiopulmonary resuscitation'/exp) AND ('hypokalemia'/exp OR 'hyperkalemia'/exp OR 'hyponatremia'/exp OR 'hypernatremia'/exp OR 'magnesium'/exp OR 'potassium'/exp OR 'calcium'/exp OR 'hypocalcemia'/exp OR 'hypercalcemia'/exp) AND (outcome OR 'mortality'/exp) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [english]/lim AND [humans]/lim

All MESH terms were exploded to include all subheadings. Citations of articles identified on primary review were reviewed. Forward search for articles citing articles identified on primary review was performed using Google Scholar.

The AHA Endnote library was searched to determine if additional relevant citations existed.

- **State inclusion and exclusion criteria**

-Included: Randomized trials, observational studies, and meta-analyses with patient oriented outcome data involving empiric treatment of cardiac arrest with electrolytes or electrolyte correction.

-Excluded: Case reports, editorials, letters to the editor. Studies that did not report relevant patient oriented outcomes. Animal studies and studies published in languages other than English.

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

The Cochrane Database Search returned 39 articles. None met the inclusion criteria above.

The EMBASE / Medline search returned 84 articles (8 unique to Medline). The titles and abstracts were reviewed for the inclusion and exclusion criteria.

Four articles met the above inclusion and exclusion criteria. (Reis is a review) {Reis, 2007 #14;Srinivasan, 2008 #11;Thel, 1997 #73;Van Walraven, 1998 #68}.

Forward search of citations of Thel: (Allegra 2001; Longstreth 2002; Hassan 2002; Sen 2006 [systematic];)

Forward search of citations of Srinivasan: (None)

Forward search of Van Walraven: (Wang 2005)

Reviewed Worksheet W101A and 101B and included fair to high quality trials with relevant patient oriented endpoints.

Found additional: Fatovich 1997, Miller 1995

Reviewed Worksheets W120, W121, and W198 which did not address treatment question.

Citation search of Reis : No unique additional trials

Citation search of Srinivasan: Stiell, 1995; Stueven 1983

Citation search of Van Walraven: No unique trials

Searched AHA Endnote Library for (magnesium OR potassium OR calcium) AND (cardiac arrest OR heart arrest)

10 studies met inclusion criteria (randomized trial or observational trial with comparison groups of unselected cardiac arrest patients [no specific presenting rhythm])

# Summary of evidence

## Evidence Supporting Clinical Question

<b>Good</b>					
<b>Fair</b>		<b>Miller 1995:3(Mg) A</b>			
<b>Poor</b>					
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Level of evidence</b>					

A = Return of spontaneous circulation  
 B = Survival of event

C = Survival to hospital discharge  
 D = Intact neurological survival

E = Other endpoint  
*Italics = Animal studies*

### Evidence Neutral to Clinical question

<b>Good</b>					
<b>Fair</b>	<b>Fatovich 1997:237 (Mg) ABC; Thel 1997:1272 (Mg) ACD; Allegra 2001:245 (Mg) AC; Hassan 2002:57 (Mg) AC; Longstreth 2002:506 (Mg) D; Reis 2008 :21(Mg) CD;</b>	<b>Miller 1995:3 (Mg) D; Stiell 1995:264( Ca) A; Wang 2005:69 (Mg/Ca) C;</b>			
<b>Poor</b>					
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Level of evidence</b>					

A = Return of spontaneous circulation  
B = Survival of event

C = Survival to hospital discharge  
D = Intact neurological survival

E = Other endpoint  
*Italics = Animal studies*

### Evidence Opposing Clinical Question

<b>Good</b>					<b>Srinivasan 2008:e1144 (Ca) CD;</b>
<b>Fair</b>		<b>Van Walvaren 1998:544(Ca) B;</b>			
<b>Poor</b>					
	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Level of evidence</b>					

A = Return of spontaneous circulation  
B = Survival of event

C = Survival to hospital discharge  
D = Intact neurological survival

E = Other endpoint  
*Italics = Animal studies*

**REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

Several contemporary randomized trials of modest size have investigated the use of Magnesium in cardiac arrest or refractory ventricular fibrillation. With the exception of an early pilot study (LOE1, Miller 1995), the other trials and a systematic review were neutral. Considering calcium – an observational study (Wang 2005) failed to show an association with improved survival. Two other observational studies (one in children) with relatively large numbers of subjects demonstrated an association between calcium administration and decreased likelihood of survival. No studies meeting the inclusion criteria addressed other electrolytes. Based on the existing data, magnesium appears to have a neutral effect on survival after cardiac arrest. No contemporary trials were relevant to the efficacy of calcium, but observational trials were neutral or associated with decreased survival. This association of calcium and decreased survival likely represents a bias of the observational study designs, since its administration tended to occur later in longer, less successful resuscitations.

**Acknowledgements:**None

### *Citation List*

**Allegra, 2001, 245**

Author: Allegra, John; Lavery, Robert; Cody, Ronald; Birnbaum, Glen; Brennan, John; Hartman, Anthony; Horowitz, Michael; Nashed, Ash; Yablonski, Michael

Year: 2001

Title: Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting

Journal: Resuscitation

Volume: 49

Issue: 3

Pages: 245-249

Short Title: Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting

*Comment: Neutral (Magnesium), LOE 1. A RCT comparing magnesium to placebo in cardiac arrest also failed to demonstrate any improvement in ROSC or survival. This trial was limited to refractory ventricular fibrillation patients.*

**Fatovich, 1997, 237**

Author: Fatovich, Daniel M.; Prentice, David A.; Dobb, Geoffrey J.

Year: 1997

Title: Magnesium in cardiac arrest (the magic trial)

Journal: Resuscitation

Volume: 35

Issue: 3

Pages: 237-241

Short Title: Magnesium in cardiac arrest (the magic trial)

*Comment: Neutral (Magnesium), LOE 1. This small RCT also did not show a benefit of magnesium in OHCA. Furthermore, as more arrests were witnessed by EMS in the magnesium group, these patients would have been expected to have a higher likelihood of ROSC and survival to hospital discharge, yet this was not observed.*

**Hassan, 2002, 57**

Author: Hassan, T B; Jagger, C; Barnett, D B

Year: 2002

Title: A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation

Journal: Emerg Med J

Volume: 19

Issue: 1

Pages: 57-62

Date: January 1, 2002

Short Title: A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation

Electronic Resource Number: 10.1136/emj.19.1.57

*Comment: Neutral (Magnesium) LOE 1. Another RCT of modest size comparing magnesium to placebo in refractory ventricular fibrillation failed to demonstrate a significant improvement in ROSC.*

### **Longstreth, 2002, 506**

Author: Longstreth, W. T., Jr.; Fahrenbruch, C. E.; Olsufka, M.; Walsh, T. R.; Copass, M. K.; Cobb, L. A.

Year: 2002

Title: Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest

Journal: Neurology

Volume: 59

Issue: 4

Pages: 506-514

Date: August 27, 2002

Short Title: Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest

*Comment: Neutral (Magnesium), LOE 1. This was a factorial design RCT comparing diazepam, magnesium and placebo in patients who experienced OHCA. Patients needed to have ROSC without complete return of neurologic function. This was therefore a study more aimed at post arrest neuroprotection. Baseline differences existed between the 4 treatment groups in this trial and no significant benefit was observed, although the absolute rates of independence and wakefulness at 3 months were higher in the magnesium alone treatment group.*

### **Miller, 1995, 3**

Author: Miller, Brian; Craddock, Lane; Hoffenberg, Steven; Heinz, Steven; Lefkowitz, Don; Lee Callender, Mary; Battaglia, Cathy; Maines, Chris; Masick, Debra

Year: 1995

Title: Pilot study of intravenous magnesium sulfate in refractory cardiac arrest: safety data and recommendations for future studies

Journal: Resuscitation

Volume: 30

Issue: 1

Pages: 3-14

Short Title: Pilot study of intravenous magnesium sulfate in refractory cardiac arrest: safety data and recommendations for future

*Comment: Supporting (Magnesium ROSC), Neutral (Magnesium Intact Neurological Survival), LOE 3. This was a pilot, open-label prospective study, investigating the administration of magnesium in refractory cardiac arrest. No difference was seen in survival to hospital discharge, and a small but not-statistically significant difference was observed in good neurological recovery in the magnesium group. Overall, the authors concluded that this was a safe treatment and further study was needed. A higher proportion of the patients who achieved ROSC in the magnesium group experienced hypotension than those in the usual care group (66% vs 42%).*

### **Reis, 2008, 77**

Author: Reis, A.G.; Paiva, E.F.d.; Schwartsman, C.; Zaritsky, A.L.

Year: 2008

Title: Magnesium in cardiopulmonary resuscitation: Critical review

Journal: Resuscitation

Volume: 77

Issue: 1

Pages: 21-25

Short Title: Magnesium in cardiopulmonary resuscitation: Critical review

*Comment: Neutral (Magnesium), LOEI (systematic review). This systematic review also sought to identify studies of magnesium that were positive and failed to do so. The conclusion that there is equipoise (no good evidence of efficacy or harm) is likely a valid one.*

### **Sen, 2006, 220**

Author: Sen, Ayan; Gidwani, Shweta

Year: 2006

Title: Intravenous magnesium in shock-resistant tachyarrhythmias

Journal: Emerg Med J

Volume: 23

Issue: 3

Pages: 220-221

Date: March 1, 2006

Short Title: Intravenous magnesium in shock-resistant tachyarrhythmias

*Comment: Neutral (Magnesium), LOEI (systematic review). This was a systematic review which did not identify magnesium as efficacious for shock resistant tachyarrhythmias.*

### **Srinivasan, 2008, e1144**

Author: Srinivasan, V.; Morris, M.C.; Helfaer, M.A.; Berg, R.A.; Nadkarni, V.M.

Year: 2008

Title: Calcium use during in-hospital pediatric cardiopulmonary resuscitation: a report from the National Registry of Cardiopulmonary Resuscitation

Journal: Pediatrics

Volume: 121

Issue: 5

Pages: e1144-1151

Short Title: Calcium use during in-hospital pediatric cardiopulmonary resuscitation: a report from the National Registry of Cardiopulmonary Resuscitation

*Comment: Opposing (calcium), LOE 5 (patient population different: pediatric inpatients.) Calcium was frequently used in pediatric in-hospital resuscitation. While controlling for prolonged resuscitation and other confounders the authors found that calcium was associated with a lower odds of survival to hospital discharge 0.6 (95% CI 0.5-0.9), lower odds of ROSC 0.8 (95% CI 0.6-1.1), and lower odds of favorable neurological outcome 0.6 (95% CI 0.4-0.8). This is suggestive that the routine use of calcium in pediatric cardiac arrest is not beneficial and may be harmful, although the others pointed out that in spite of a 2000 AHA recommendation that stated the former – over 40% of pediatric cardiac arrest patients received calcium. Extrapolation to adults is difficult, as the epidemiology of cardiac arrest is different, however this provides additional information that fails to show efficacy, and raises the possibility of potential harm.*

### **Stiell, 1995, 264**

Author: Ian G. Stiell, George A. Wells, Paul C. Hebert, Andreas Laupacis, Brian N. Weitzman,

Year: 1995

Title: Association of Drug Therapy with Survival in Cardiac Arrest: Limited Role of Advanced Cardiac Life Support Drugs

Journal: Academic Emergency Medicine

Volume: 2

Issue: 4

Pages: 264-273

Short Title: Association of Drug Therapy with Survival in Cardiac Arrest: Limited Role of Advanced Cardiac Life Support Drugs

*Comment: Neutral (Calcium) LOE2. This observational study sought to examine associations with administration of various ACLS medications with successful resuscitation. Given the sample size and multiple interventions studied, this study had limited power to detect any beneficial or harmful effect of calcium administration.*

### **Thel, 1997, 1272**

Author: Thel, M.C.; Armstrong, A.L.; McNulty, S.E.; Califf, R.M.; O'Connor, C.M.

Year: 1997

Title: Randomised trial of magnesium in in-hospital cardiac arrest

Journal: Lancet

Volume: 350

Issue: 9087

Pages: 1272-1276

Short Title: Randomised trial of magnesium in in-hospital cardiac arrest

*Comment: Neutral (Magnesium), LOE 1. This was an RCT focused on in-hospital cardiac arrest, comparing magnesium to usual care. Again, magnesium administered empirically in cardiac arrest did not improve any relevant patient oriented outcomes.*

### **Van Walraven, 1998, 544**

Author: Van Walraven, C.; Stiell, I.G.; Wells, G.A.; Hebert, P.C.; Vandemheen, K.

Year: 1998

Title: Do advanced cardiac life support drugs increase resuscitation rates from in-hospital cardiac arrest?

Journal: Annals of Emergency Medicine

Volume: 32

Issue: 5

Pages: 544-553

Short Title: Do advanced cardiac life support drugs increase resuscitation rates from in-hospital cardiac arrest?

*Comment: Opposing (calcium), LOE 2. This prospective cohort study of in-hospital cardiac arrest patients found no association with improved resuscitation for any standard ACLS medication. The administration of calcium was significantly associated with a higher likelihood of unsuccessful resuscitation. The potential explanations for this are many. Conceivably the patients who received calcium may have been at late stages in resuscitation, where "everything" was been attempted. These patients may have represented a subset of the cohort that was unsalvageable. It also is possible that higher rates of renal failure and hyperkalemia were evident in the patients administered calcium, as cardiac arrest associated with these conditions is less survivable.*

### **Wang, 2005, 69**

Author: Wang, Henry E.; Min, Alice; Hostler, David; Chang, Chung-Chou H.; Callaway, Clifton W.

Year: 2005

Title: Differential effects of out-of-hospital interventions on short- and long-term survival after cardiopulmonary arrest

Journal: Resuscitation

Volume: 67

Issue: 1

Pages: 69-74

Short Title: Differential effects of out-of-hospital interventions on short- and long-term survival after cardiopulmonary arrest

*Comment: Neutral (Magnesium and Calcium), LOE 2. In this retrospective evaluation of a database of cardiac arrest patients from a defined geographical area, calcium and magnesium were not associated with an increased likelihood in survival. Overall, each agent was used in roughly 10% of arrests.*