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

**Worksheet author(s)**

| Dianne Atkins, MD |

**Date Submitted for review:**

April 23, 2008, Revision August 1, 2008  R 2 1-22-09

**Clinical question.**

In pediatric patients with cardiac arrest (pre-hospital [OHCA] or in-hospital [IHCA]) due to VF/pulseless VT (P), does the use of amiodarone (I) compared with lidocaine (C), improve outcome (e.g., ROSC, survival to hospital discharge, survival with favorable neurologic 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 of existing worksheet

**Conflict of interest specific to this**

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

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

**PubMed:**

3. ("Amiodarone"[Mesh]) OR ("Lidocaine"[Mesh]) AND ("Death, Sudden, Cardiac"[MeSH Major Topic]) OR ("Heart Attack"[MeSH]) AND ((Humans[Mesh]) AND (adult[MeSH:noexp] OR middle age[MeSH])) 204 references
5. (Amiodarone OR Lidocaine) AND ventricular fibrillation AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract] OR cohort[Title/Abstract]) 109 references, none used
6. (Amiodarone OR Lidocaine) AND resuscitation AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) 24 references

**Cochrane**

Amiodarone, Title, Abstract, Keyword 0 references
Lidocaine, Title, Abstract, Keyword 0 references
Cardiac Arrest Title, Abstract, Keyword 0 references
Ventricular tachycardia Title, Abstract, Keyword 0 references
Ventricular fibrillation Title, Abstract, Keyword 0 references

**Science Citation**

Kudenchuk PJ NEJM 1999 178 citations
Dorian P. NEJM 2002 98 citations
EMBASE
Amiodarone and cardiac arrest 200 citations
Lidocaine and cardiac arrest 133 citations

**State inclusion and exclusion criteria**

**Inclusion criteria:**

- Use of amiodarone or lidocaine in all ages
- Use of amiodarone in children with ventricular arrhythmias, not just pulseless ventricular tachycardia or ventricular fibrillation

**Exclusion criteria:**

- Amiodarone used for prevention of SCD or ventricular arrhythmias
- Animal studies
- Amiodarone or Lidocaine use in other than ventricular arrhythmias

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

7 All publications were from adult populations. Only one was 1 prospective randomized trial. All others were retrospective reviews. Two papers compared lidocaine with drugs not available in the United States, but share similar antiarrhythmic properties.

The papers reviewed from the 2005 Guidelines, including the 2 RCT which heavily influenced the 2005 recommendations, are included on the grid and the citation list. The summary discussion or the 2005 Guidelines is also included.
# Summary of Evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Evidence Supporting the Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td>Kudenchuk 1999 B, Dorian 2002 B, Somberg 2002 AB</td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>Bogers AJ 87 AB, Perry, 1993 B</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*

## Evidence Neutral to Clinical Question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td>Kovoor 2005 E, C, Kowey, 1995 B, Haynes 81 A, C</td>
</tr>
</tbody>
</table>

### Level of Evidence

- **A** = Return of spontaneous circulation
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*Italics = Animal studies*
Evidence Opposing Clinical Question

<table>
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<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<td>4</td>
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Level of evidence

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

This worksheet is an update of a question evaluated in 2005. The URL for those worksheets are:
http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.170522/DC29
http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.170522/DC30
http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.170522/DC31.

Many of the references from 2005 are included in this worksheet for reference. References with animal studies were excluded. The two references cited in the 2005 guidelines and which served as the major support for the current recommendations are included in the worksheet. The discussion here focuses on the new references as there has been little data published to support a change.

In the 2005 Guidelines statement for adult and pediatric advanced life support, amiodarone for shock resistant (after 3 shocks and one dose of epinephrine) is recommended (Class IIb, LOE3,7). Lidocaine is to be used if amiodarone was not available. Support for amiodarone derived from improved hospital admission over both placebo and lidocaine. Neither study was powered to detect differences in hospital discharge.

Since publication of the 2005 Guidelines, only minimal pediatric or adult data have been published. There has been one pediatric study evaluating outcomes of in-hospital ventricular tachycardia or fibrillation from the National Registry of CPR (Samson 2006). The primary outcome was survival to hospital discharge with secondary outcomes of ROSC for 20 minutes and neurologic outcome. Antiarrhythmic use, specifically amiodarone, lidocaine or procainamide were included in the multivariate analysis, but none were significant.

There have been no additional randomized trials of amiodarone vs. lidocaine, although there have been two studies of other Class III drugs vs. lidocaine. (Kovoor, 2005,Tahara, 2006) There has been one multicenter retrospective chart review comparing amiodarone vs. lidocaine vs. both drugs. (Rea, 2006).

**Summary of data published since the 2005 Guidelines**

Rea et al examined 194 patients who received amiodarone, lidocaine or both. The endpoint was alive at 24 hours or hospital discharge. No significant differences could be detected among the three groups, but several explanations were provided for lack of efficacy. The most important were that the average amiodarone dose was 190 mg, not the recommended 300 mg and the time from collapse to drug administration was longer for amiodarone compared to lidocaine.

Pollak’s study is also a retrospective review of amiodarone use for in-hospital arrest with end-points of ROSC, time not defined and hospital discharge. For 374 patients, there was no statistical difference between amiodarone and lidocaine for either endpoint. A conditional power analysis was also performed, which also did not predict any benefit to amiodarone.
Herlitz’ data was published in 2003, but was not cited in the worksheet used by the pediatric committee. Lidocaine given in the emergency department had an OR of survival of 1.64 (95% CI 1.27, 2.11). When given to out-of-hospital arrest patients with VF, lidocaine had a beneficial effect on n after 4 defibrillatory shocks were compared to those who did not receive the drug.

The other two papers compare two Class III anti-arrhythmics (K channel blockers) which are not currently available in the US: nifekalant and intravenous sotalol. Nifekalant improved admission to hospital and 24 hour survival compared to lidocaine, but there was no difference in hospital discharge. There was no difference in hospital admission or survival between IV sotalol and lidocaine. Both studies enrolled approximately 120 patients, so were also underpowered.

Prior summary of data reviewed for the 2005 Guidelines:

1. No data are available to specifically answer the question: Is amiodarone effective and safe in shock resistant or refractory VT/VF in children? The published articles evaluating amiodarone in children concentrate on treatment of refractory arrhythmias, both atrial and ventricular in children.(Perry 1996, 1993, Figa, 1994) Effectiveness in this diverse group of patients is good and side effects are low. However, most of these patients were treated with intravenous amiodarone while it was investigational and thus the infusions were well controlled and virtually all observed by a pediatric electrophysiologist. None of the patients was treated with rapid IV boluses and none was treated during a cardiac arrest. Side effects, especially hypotension, may be more significant when amiodarone is given quickly under even more emergent conditions than these.

2. Data for other frequently used or potential anti-arrhythmic medications (procainamide, lidocaine, bretylium and magnesium) in pediatric resuscitation are even more limited, or non-existent. The review in 2000 produced virtually no studies specific to children. A very extensive review by Dr. Kudenchuk revealed that most of the studies of lidocaine in adults were LOE 4 and greater (only 2 were LOE 2) and the quality of the evidence was judged as good to fair. Many of the studies were neutral or opposed the use of lidocaine.

3. There are now 2 randomized blinded controlled trials of amiodarone use in refractory out-of-hospital ventricular fibrillation, one placebo controlled (Kudenchuk, 1999,) the other comparing amiodarone to lidocaine (Dorian, 2002). Kudenchuk’s study compared 300 mg IV push amiodarone after 3 shocks plus epinephrine to placebo. 246 patients received amiodarone and 258 received placebo. Resuscitations were prolonged (42-43 minutes) and 5-6 shocks were delivered. More patients receiving amiodarone than placebo were admitted to the hospital (44% vs. 34%) p=0.03. Hypotension was more common in the amiodarone treated group. The study was underpowered to detect a difference in hospital discharge. Dorian’s study design was similar: patients were treated with amiodarone or lidocaine after 3 shocks, then epinephrine and an additional shock for recurrent VF. A total of 347 patients were enrolled. Again the rate of hospital admission was improved in the amiodarone treated group, but overall percentages were low: 22.8% amiodarone vs. 12% lidocaine admitted to the hospital. If the time to administration of amiodarone was < 25 minutes from dispatch, the rate of admission to hospital rose to 27.7% compared with lidocaine 15.3% (p=0.03) No difference in hospital discharge rate could be demonstrated, but the numbers were quite small: of 41 patients admitted only 9 (5% of the entire group) survived to hospital discharge. Based on these studies amiodarone appears to be the superior agent for shock resistant VT/VF. A third RCT study comparing aqueous amiodarone to lidocaine in the treatment of shock resistant ventricular tachycardia also demonstrates superiority of amiodarone to lidocaine. (Somberg 2002).

4. The data for effectiveness and safety of amiodarone in adults with in-hospital refractory VT/VF, include randomized double-blind controlled trials (usually with varying doses or alternative drugs, not placebo controlled.(Scheinman, 1995, Kowey, 1995, Levine, 1966) Effectiveness, usually defined as a decrease in the number of events or longer intervals between events, has been demonstrated in 2 studies and lack of serious toxicity (i.e. less effective than control medication or toxic effects of amiodarone) in the remainder. Improved survival to discharge has not been documented.

5. Although lidocaine has had broad use and acceptance, there are minimal data to support its use. Until recently, the recommendations have not been submitted to placebo-controlled trials. Only one study supports its use (Herlitz, 1997), the rest are not relevant or neutral especially given changes in protocols (Haynes, 1981, Olson 1984) and two RCTs show that lidocaine is inferior to IV amiodarone (Dorian, 2002, Somberg 2002).

6. It is unlikely that any studies will be performed on use of amiodarone in emergency situations for children, so we will be forced to rely upon extrapolation of adult data.
As neither the pediatric nor adult data indicate a clear benefit for either drug, there is no scientific evidence to support a change in the recommendation.

Acknowledgements:

Citation List


LOE 4, Poor. Single case report of treatment of a neonate with VF arrest after cardiac surgery. Article in German and not available to me.


LOE is 5, RCT. Subjects were adults supportive of amiodarone, negative for lidocaine directed at the specific question, but data must be extrapolated to children. Patients treated with amiodarone were twice as likely to survive to hospital admission that patients treated with Lidocaine. The earlier the patients received the amiodarone, the better their survival.


LOE is 5 (extrapolated data since ventricular arrhythmias were not pulseless. good, supportive of amiodarone). Case series, not controlled. Amiodarone was effective at treating ventricular arrhythmias in children with IV load and constant infusion. LOE 7 because patients did not suffer cardiac arrest.


LOE 5 (excellent, adults, neutral for lidocaine) Study drug was randomly administered after one 320 J shock. No chemical defibrillation was observed. There was no difference between the two drugs. Patients who received lidocaine required a “standard” number of shocks and 26% were discharged from the hospital.


LOE is 5 (fair, adults, supportive of lidocaine). Adult out-of-hospital sudden cardiac arrest. Patients who received IV lidocaine were compared with those who did not. Patients who received IV lidocaine had higher rates of ROSC and hospital admission. No difference demonstrated in hospital discharge.


LOE 5 (adult population and retrospective stud) 20 year experience in well-studied EMS system. Children < 8 are included but comprise < 10% of the study group. No breakdown of rhythm treatment, etc based on age. Beneficial effect of lidocaine documented only in the ED. IT is not clear is EMS providers were able to give lidocaine.

LOE 5 (Population, different anti-arrhythmic) blinded RCT of sotalol and lignocaine (lidocaine) in adults with out-of-hospital refractory ventricular fibrillation. There was no difference in hospital admission or survival to discharge between the two groups. Sotalol has significant class III activity but also has significant beta blocking activity.


LOE 5 (good, adults, neutral for amiodarone) as it is a randomized blinded trial. The study compares amiodarone to bretylium, which is no longer recommended or manufactured. The dose of amiodarone which was most effective is substantially higher than that currently recommended


LOE is 5 (population) Subjects were all adults so data is extrapolated to children. RCT directed at the specific question. Patients who received amiodarone had a higher survival to hospital admission but survival to hospital discharge could not be tested due to insufficient power.


LOE 5, Fair Supportive. Literature review of best drug for refractory VF/VT after cardiac surgery. One case report of an infant in whom amiodarone was effective and lidocaine was not. Most references are cited in the worksheet. Final recommendations basically are derived from 2005 recommendations, recognizing limitations of the randomized trials and final recommendations a consensus statement.


Level 5 (poor, adult patients who were hypotensive and unresponsive to lidocaine, procainamide or bretylium, but not pulseless. No control group. Primary aim of study was to determine 24hour dose to prevent recurrence.)


LOE is 5 (fair, adults, neutral for amiodarone). Patients with recurrent ventricular arrhythmias treated with bolus amiodarone and then a constant infusion. Significant adverse events of hypotension and pacer dependent bradycardia were apparent despite effectiveness at terminating VT. Patient who received amiodarone had better survival to hospital discharge.

LOE 5 (good, adults, neutral for lidocaine) AHA protocol at this time was 2 shocks with 200 J then given a drug. No clear distinction between the drugs was observed. Hospital discharge was higher in the lidocaine treated group but this was not statistically significant.


LOE is 5 (poor, supportive of amiodarone). Small case study, not controlled. Amiodarone effective at treating children with post-operative ventricular arrhythmias. Rhythms were associated with life-threatening hypotension, but patients were not pulseless and no patient had ventricular fibrillation.


LOE is 5 (Extrapolated information since several patients had ventricular tachycardia, but not necessarily pulseless. good, supportive of amiodarone). Patients had post-operative arrhythmias; there were no controls. Patients were children. Amiodarone was successful at controlling 58% of the patients with ventricular arrhythmias. Patients were loaded with amiodarone over 1 hour and then given IV infusion.


LOE 5 (population, retrospective study) Retrospective study on in-hospital use of amiodarone following 200 guidelines No survival benefit between amiodarone and other anti-arrhythmic drugs, primarily lidocaine but also included bretylium


LOE 5 (Population, retrospective) Multicenter study. Patient population is adults > 18 year experiencing in hospital cardiac arrests. Patient groups well–defined Includes patients with initial VT/VF as well as initial bradycardia with subsequent VT/VF. No survival advantage (24 hour or hospital discharge) to amiodarone, lidocaine or both drugs. Potential explanations include inadequate dosing of amiodarone, longer time interval to amiodarone dosing compared to lidocaine, longer time to defibrillation in amiodarone population.


LOE 2 (pediatric cardiac arrest patients with survival outcome) Prospective cohort studies with concurrent controls. Data derived from well established multi-center database with good quality control mechanisms in place. Primary purpose of paper was to evaluate outcomes of initial or subsequent ventricular fibrillation, and determine factors associated with survival.


LOE is 5 (good, adults, supportive of amiodarone). Although it is a randomized blinded trial, the subjects were adult patients with life-threatening ventricular arrhythmias and not necessarily shock resistant in the strict definition. Many of the patients had recurrent episodes over a several hour period. Dose of amiodarone in 2 groups was higher than currently recommended. However, results were encouraging in that number of subsequent episodes of VT/VF after amiodarone were significantly less

LOE is 5(excellent, adults, supportive of amiodarone). Randomized controlled trial of aqueous amiodarone and lidocaine for treatment of incessant, shock resistant VT. Aqueous amiodarone is currently not available. Its purported advantages are less hypotension due to the difference in the diluent. The electrophysiologic effects are the same as the commercially available amiodarone. Amiodarone was more effective than lidocaine at terminating shock resistant VT.


LOE 5 (population, retrospective, Type III anti-arrhythmic but not amiodarone) Out-of hospital cardiac arrest. Primary endpoint was admission to hospital and 24 hour survival. Neurological intact at discharge was reported. Nifekalant increased hospital admission and 24 hour survival compared to lidocaine. Note: Nifekalant is a pure K channel blocker with minimal negative inotropic effects and it lowers defibrillation threshold while amiodarone increases it. Lidocaine increases defibrillation energy requirements.


LOE is 5 (fair, adults, neutral for lidocaine) Lidocaine was associated with poorer survival in out-of hospital cardiac arrest. However, this was uncontrolled, patients received many ACLS drugs and none were associated with survival.


LOE 5 (Population, Retrospective) Paper is in German, English abstract. Inadequate analysis of data.


LOE is 5 (fair adults, neutral for lidocaine). Lidocaine was associated with a threefold increase in asystole after defibrillation shocks. Although lidocaine appeared to have a negative effect, this was attributed to delay in defibrillation rather than a direct effect of the drug.