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

**Worksheet author(s)**

| Swee Han Lim | Date Submitted for review: 02 September 2009 |

**Clinical question.**

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

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** The question is addressing a therapy.

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

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

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

Atropine AND asystole or pulseless electrical activity or cardiac arrest keyword search for all databases. PubMed, MedLine, MedScape, Cochrane, MDConsult, AHA EndNote 7 Master library Embase selected references from searched articles were reviewed.

**State inclusion and exclusion criteria**

Only clinical studies on human and animals dealing with treatment of cardiac arrest with atropine were included. Excluded review articles, case reports < 5 patients, manuscripts with bradycardia patients only, patient not in cardiac arrest.

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

17 articles met criteria for review.

- Brown 1979
- Coon 1981
- Redding 1983
- Sorensen 1984
- Stueven 1984
- Tortolani 1989
- Blecic 1992
- DeBehnke 1995
- Stiell 1995
- van Walraven 1998
- Engdahl 2000
- Lovstad 2000
- Niemann 2000
- Dumot 2001
- Engdahl 2001
- Niemann 2002
- Stiell 2004
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
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- **Stueven 1984**
- **Brown 1979**
- **Sorensen 1984**
- **Lovstad 2000**
- **Niemann, 2000**
- **Niemann, 2002**

**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

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<tr>
<td>Fair</td>
<td>Stiell 2004&lt;sup&gt;C&lt;/sup&gt;</td>
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<td>Coon 1981&lt;sup&gt;A,B,C,E&lt;/sup&gt;</td>
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A = Return of spontaneous circulation  
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### Evidence Opposing Clinical Question

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| Poor | Van Walraven 98  
Dumot, 2001<sup>C</sup>  
Engdahl 2001<sup>C</sup>  
Engdahl, 2000<sup>C</sup> |  |  |  |  |

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A = Return of spontaneous circulation  
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**REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

There is no level 1 study (randomized clinical trial) to show intravenous (IV) atropine improved survival in patients with asystole or pulseless electrical activities.

Evidence from three level 4 studies (case series) Brown 79, 448, Sorensen 84, 232, Lovstad 00, 48 (total of 12 OR, 2 cath lab, 2 OHCA, 4 IHCA patients) documented improvement in survival when atropine was administered to asystole patients. For the 2 OHCA and 4 IHCA patients, CPR was started within 5 mins. All the above studies were rated as poor quality because the sample size was very small. In OR setting, most patients did not have heart disease and were very closely monitored. The conclusion drawn from these studies may not be generalised to OHCA or IHCA setting.

Evidence from one level 3 study (Stueven 84, 815) documented improvement in ROSC (14% vs 0%) when atropine is administered to 41 OHCA asystole adults compared with 129 patients who did not receive atropine. None of 170 patients survived to discharge.

Two retrospective studies comparing OHCA asystole adults received IV epinephrine and IV atropine vs endotracheal (ET) epinephrine and atropine. Niemann 00, 1815 (136 patients, 57% received IV atropine/epinephrine, 43% received ET drugs) Niemann 02, 153 (596 patients, 83% received IV atropine/epinephrine, 17% received ET drug). Improvement in rate of ROSC was documented in OHCA asystole adults when IV epinephrine and IV atropine were given, compared with endotracheal epinephrine and atropine. Niemann 2002 also showed improvement in survival to hospital discharges in the IV drug group (5%) compared with ET drugs (0%, p=0.001). It was not clear whether the beneficial effect was derived from IV epinephrine or from IV atropine. It was also not clear why some patients were given ET drugs instead of IV drugs.

Evidence from one level 2 study (Stiell 04c, 647) before and after controlled trial showed that the additional of ALS interventions including IV drug (n= 4247) did not improve the rate of survival OHCA in a previously optimised EMS of rapid defibrillation EMS (n= 1391). (ALS group 95.8% given IV epinephrine, 87.3% given IV atropine, Initial rhythm VF 31.5%, PEA 25.3%, asystole 42%)

One level 2 (Coon 81 A, B, C, E, 462) and two level 5 (Tortolani 89B, 622, Stiell 95C, 264) studies suggested that the use of atropine for treatment of cardiac arrest was not associated with improved/decreased survival.

Coon 81: OHCA 21 asystole or PEA; 100% received atropine
Tortolani 89: IHCA, n=630, 82% received atropine, initial rhythm asystole 24%
Stiell 95: OHCA, n=529, 66% received atropine

Four level 5 (Dumot 01c, 1751, Engdahl 00c, 610, Engdahl 01C, 17, Van Walraven 98B, 544) human studies suggested that the use of atropine was associated with poor survival.

Dumot’s 01 and Van Walraven 98 study was on all types of rhythms in IHCA. Studies on the efficacy of atropine in the treatment of asystole is confounded by the fact that asystole is associated with poor outcome.

Van Walraven 98: n= 733, VF 32%, PEA 40%, asystole 28%, 79% of patients received atropine associated with decrease discharge survival OR 0.24 (0.17-0.35).

Dumot’s 01: n=482. did not mention initial rhythm percentage of VF, PEA, asystole and how many patients received atropine. Engdahl’s 00 and 01 studies were on OHCA asystole and PEA respectively. These studies documented survivors received atropine less often on scene compared with non survivors.

All the above studies did not mention why some of the patients did not receive atropine.

One level 5 animal study (canine model of asphyxial PEA) suggested that standard dose atropine did not improve ROSC rate compared with placebo. Increasing doses of atropine tended to decrease ROSC rates.

**Acknowledgements:** Munish Goyal, MD, who done 2005 worksheet on usage of atropine 1 mg IV, repeated every 3 to 5 minutes up to a total of 0.04 mg/kg in asystole improve patient outcomes.
## Citation List

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Comments: Level 5 (PEA not asystole); fair. Neutral. Small prospective, controlled, blinded canine countershock PEA model. Each animal was submitted to two successive episodes of CPR, one including repeated injections of atropine and one including repeated injections of D5W at the same time intervals. The order of the two CPRs was randomized. Only 30 minutes allowed between two episodes. Atropine dose ~ 0.025mg/kg/dose. All animals received epinephrine. Short duration of cardiac arrest with CPR initiated 4 minutes after loss of circulation and study drug administered 9 minutes after loss of circulation. Trend towards increase ROSC in atropine group. Atropine group with statistically significant increase in heart rate, stroke volume, systolic and diastolic blood pressure, and cardiac output in addition to decreased time to recovery. |
Comments: Level 4; poor. Supportive. Small case series of 8 asystolic patients. Six patients in-hospital (including 2 who developed asystole during cardiac catheterization), 2 out-of-hospital. All responded within 30 seconds of atropine administration. 2 patients received only atropine after becoming asystolic during cardiac catheterization. Three patients survived to hospital discharge (including 2 who developed asystole during cardiac catheterization). Dose ranged between 0.5 – 2.0 mg. All patients had CPR started within 5 minutes of cardiac arrest. |
Comments: Level 2; poor. Neutral. Small prospective, controlled, non-randomized study of out-of-hospital cardiac arrest patients. Study did not mention how treatment group and control group were assigned. Showed no difference in rhythm change, ROSC, survival to admission, or survival to discharge in control versus atropine groups. Combined asystole and slow PEA patients into one group. Administered sub-therapeutic doses of atropine (1-2 mg). No control of additional therapies used. |
Comments: Level 5 (PEA not asystole); fair. Neutral. Small prospective,
controlled, blinded canine asphyxial PEA model. 15 dogs per group received either saline or an escalating dose of atropine after the equivalent of approximately 22 minutes of down-time (10 minutes in PEA). No difference in ROSC or survival rates noted between standard dose atropine and placebo groups.

**Dumot 2001**


Level 5, Poor. Opposing.

Comment: This was an in-hospital cardiac arrest study. Did not mention how many percent of patients not given atropine and the reason for not administering atropine.

**Engdahl, 2000**


Level 5, Poor. Opposing. It was mentioned why 56% of patients did not receive atropine.

**Engdahl, 2001**


Level 5, Poor. Opposing.

There was an association between survival outcome (survival to discharge) and treatment with atropine (better outcome if treatment was not given; p=0.007). Only 18% of patients received atropine. The study did not mention the reason of not administering atropine.

**Lovstad 2000**


Comments: Level 4; poor. Supportive. Case series of 5 patients depicting 5 otherwise healthy patients getting minor procedures with the complication of asystole or severe bradycardia (HR of 20 without a blood pressure). All patients were given a combination of atropine and ephedrine or adrenaline with prompt ROSC. Unclear which medication caused ROSC.

**Niemann, 2000**


Level 5, poor. Supportive.
If we regard ET atropine and adrenaline as placebo, this study had shown that intravenous adrenaline and/or atropine increase rate of return of spontaneous circulation of out-of-hospital primary and post-counter shock asystole, but did not improve survival. We cannot be sure of relative effectiveness of adrenaline from atropine as patients were given both drugs.

**Niemann 2002**


Level 5, Poor. Supportive.

This study showed that intravenous (IV) ACLS medications (adrenaline and atropine) did improve survival of our-of-hospital cardiac arrest compared with endotracheal (ET) ACLS medication. For ET group, patients were administered doses equal to twice the recommended IV dose. Effect of ET medication might be considered as placebo as Quinton had showed that there no change in adrenaline level after ET administration compared to a three-fold increase in patients who received the drug intravenously.

The main confounding factor in this study was that in the ET drug group, a significantly greater number of patients had an initial documented asystole arrest compared to the IV drug group (56 vs 37%, p=0.07) had more VF/VT arrest.

**Redding 1983**


Comments: Level 5 (PEA not asystole); fair. Neutral. Small prospective, controlled trial using an asphyxial canine PEA model to compare methoxamine to saline, atropine, and calcium chloride. Flawed by using 0.5 mg dose of atropine (0.02 – 0.045 mg/kg) and not using any epinephrine. 5 of the 10 dogs receiving atropine had ROSC compared to 2 of the 10 controls (saline). A prompt response signifying pharmacologic effect, however, was not noted.

**Sorensen 1984**


Comments: Level 4; poor. Supportive. In OR setting, the patient did not have heart disease and are very closely monitored. IV atropine was given promptly. Asystole in operating room setting may not generalize to OHCA or IHCA setting. *Abstract-only available for review.

**Stiell, 1995**


Level 5, Fair. Neutral.
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<tr>
<td>Intravenous atropine was administered to 87.5% of the patients in the advanced life support phase.</td>
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<td>Comments: Level 3; poor. Supportive. Retrospective review of prehospital refractory asystolic patients. Asystole defined as refractory when patient remains asystolic after receiving epinephrine and sodium bicarbonate. All patients were endotracheally intubated and had an intravenous line established. 14% of patients who received atropine survived to ED admission compared to zero patients who did not receive atropine. No comment was given for why 41 patients (control group) did not receive atropine. Although both groups had comparable age, sex, witnessed arrest, cardiac history and cardiac drug use, no comment is made on down time or bystander CPR rates. Drug dosages not listed. No patient with refractory asystole was discharged alive.</td>
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<td>Patients who received a pacemaker (N=60) were less likely to survive than those who did not (13.3 percent vs 33.9 percent; p&lt;0.01). Among those who received norepinephrine and lidocaine drips in addition to the AHA-recommended epinephrine and atropine (N=12), 58.3 percentage survived 24 h while only 12.3 percentage of those who received epinephrine and atropine but not norepinephrine and lidocaine (N=73) survived (p&lt;0.01). The overall statistical difference in 24 h survival between those patients who received the AHA-recommended procedures (N=85, 18.8 percent survived) and those who did not (N=35, 34.3 percentage survived) was not significant (p=0.07).</td>
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<td>Comments: Level 5; poor. Opposing. Prospective observational cohort study of in-hospital cardiac arrest patients. ACLS drug administration compared between survivors (to one hour) and non-survivors. Found that use of ACLS drugs (including atropine) was associated with unsuccessful resuscitation. I think prolonged resuscitation is associated with increased...</td>
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administration of ACLS drugs. It is to be expected that if a patient is not responding to initial interventions, one would continue down the resuscitation algorithm.