Clinical question.

Fuchs and Kurosawa: In infant and children with bradycardia that unresponsive to oxygenation and/or ventilation (P), does the use of atropine (I), as compared with epinephrine (C), improve patient outcome (return to age-appropriate heart rate, subsequent pulseless arrest, survival) (O)?

Nitta: In infants and children with cardiac arrest (out-of-hospital and in-hospital) or symptomatic bradycardia (P), does the use of atropine (I) compared with no atropine use (C), improve outcome (O) (eg. ROSC, survival)?

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

State if this is a proposed new topic or 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).

Fuchs (052A):
Embase: bradycardia, atropine, epinephrine: 47 articles- none useful
Embase June 4, 2009: bradycardia, epinephrine, atropine: 11 articles from combined search-none useful, 21 from bradycardia and epinephrine-1 useful-had already, 108 from bradycardia and atropine-1 useful-had already
Pubmed: bradycardia (mesh), atropine(mesh), atropine derivative(mesh), epinephrine(mesh) 31 articles results- none were useful
Cochrane library: bradycardia (mesh), epinephrine (mesh), atropine (mesh): 97 articles, 1 useful (epinephrine for the resuscitation of apparently stillborn or extremely bradycardic newborn infants AJA Zino, MW Davies, PG Davis Cochrane Database of Systemic Reviews 2002, Issue 3, Art no: CD003849.
Cochrane library June 4, 2009- no additional information that previously Pubmed: bradycardia (mesh), atropine(mesh), atropine derivative(mesh), epinephrine(mesh) : 69 articles, 5 possibly useful

Hand searching references of articles
Review of 2005 ILCOR worksheets on similar topic
Recommendation from Dr Morley

Kurosawa (052B): Databases searched: Medline, ECC EndNote Master Library
Previous 2005 WS related to this question was reviewed and added several hand search.

#1 Bradycardia, Atropine, Child → hits 122
#2 Bradycardia, Epinephrine, Child → hits 25
#3 #1 OR #2 → hits 136 → 1 article(#1)
#4 Bradycardia, Resuscitation, Atropine → hits 81
#5 Bradycardia, Resuscitation, Epinephrine → hits 72
#6 #4 OR #5 → hits 119 → 4 article(#2 - #5)

#9 #7 OR #8 → hits 53, but there is no appropriate article.

#10 What is the optimal drug therapy for significant bradycardia? (WS91 Lim Swee Han, 20 Oct 2004) → 2 articles(#6, #7)
#11 Additional hand search → 2 articles(#8, #9)

Nitta (042B):
Databases searched: MEDLINE, Cochrane, ECC EndNote Master Library
Previous 2005 WS related to this question was reviewed and added several hand search.

#1 "Heart Arrest"[Mesh] AND "Atropine"[Mesh]
#2 "bradycardia"[Mesh] AND "Atropine"[Mesh]
#3 #1 OR #2 advanced search child: 0-18 years
#4 #2 and (symptomatic bradycardia or resuscitation or shock or cardiopulmonary failure)
#5 "Heart Arrest"AND "Atropine"
#6 "symptomatic bradycardia" AND "Atropine"
#7 #5 or #6 advanced search child: 0-18 years
#8 Additional hand search

• **State inclusion and exclusion criteria**
  Fuchs: None
  Kurosawa: Included all human clinical trials, meta-analysis, case reports, guidelines. English only.
  Review articles and animal experiments were excluded.
  Nitta: The following studies were excluded: Not true cardiac arrest cases.
  Included all human clinical trials, meta-analysis, and animal experiments. English Language limitations.
  Review articles were excluded.

• **Number of articles/sources meeting criteria for further review:**
  Fuch: 12
  Kurosawa: 9 articles relevant to the topic (from 308 hits and previous WS) were reviewed in detail
  Nitta: **Number of articles/sources meeting criteria for further review:**
  #3 9 articles relevant to the topic (from 123 hits)
  #1 17 articles relevant to the topic (from 183 hits)
  #4 4 articles relevant to the topic (from 57 hits)
  #7 9 articles relevant to the topic (from 85 hits)
  #8 2 articles relevant to the topic
  #3 or #1 or #4 or #6 or #8 22 articles relevant to the topic and 12 articles were reviewed in detail
# Summary of evidence

Studies in **Bold**-Fuchs  
Studies in Normal font-Kurosawa  
Studies in *Italic*- Nitta  
Studies in **Bold** and Underlined-Fuchs and Kurosawa  
Studies in **Bold & Italic**- Fuchs and Nitta  
Studies in *Italic* and underlined-Kurosawa and Nitta  
Only study cited in all 3 (**bold, italics and underlined**) - Coon

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
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<td><em>Italics = Animal studies</em></td>
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## Evidence Neutral to Clinical question

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### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
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<tr>
<td>* Pediatric Study</td>
<td>Horigome E *</td>
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<td>Herlitz 1994 (BCE) Herlitz 2003 (BCE) Engdahl (BCE)</td>
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<td>Tibballs (ABCD) Guay (ABCD) Reis (ABCD) DeBehnke (A) Coon (ABCE)</td>
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**Level of evidence**

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

* Pediatric Study
Fuchs: There were no randomized controlled, quasi-randomized controlled trials or any study in children which looked at the specific question: In infants and children with bradycardia that is unresponsive to oxygenation and/or ventilation, dose the use of atropine as compared to epinephrine improve patient outcome.

The studies that were supportive of atropine in some aspect include the case series by Brown (LOE 5) which involved 8 adults in cardiac arrest, all whom were in asystole as the initial rhythm or as a result of defibrillation. Six failed to respond to epinephrine, but responded to atropine. And 50% of these patients were discharged from the hospital. In the prehospital study by Stueven (LOE 5), which was a retrospective review, there were 84 adult patients in asystole who remained in asystole after epinephrine (and sodium bicarbonate). Of these patients, 43 also received atropine, and 6 had successful resuscitation, which was defined as conveyance of a patient with a rhythm and pulse to an emergency department vs 0/41 of the epinephrine, sodium bicarbonate group, (P<.04). However, none of the patients who received atropine survived to hospital discharge. Therefore, this study is neutral with respect to survival to hospital discharge.

The only pediatric study to support the use of atropine involved 4 infants who had undergone cardiac surgery (Fullerton LOE 4). Three experienced hypotension, followed by bradycardia and asystole. Two did not respond to epinephrine, but all responded to atropine. One other infant had episodes of hypotension without bradycardia, and responded to atropine. It was thought that these episodes were secondary to the Bezold-Jarisch reflex. This reflex is initiated by activation of mechanical stretch receptors located mainly in the wall of the left ventricle, with afferents carried by the right vagus nerve. Activation of this reflex results in hypotension and bradycardia mediated by cholinergic vasodilatation and withdrawal of sympathetic tone. The continuous administration of atropine in all cases prevented the recurrence of this reflex in these patients. This concept may support the use of atropine in vagally mediated bradycardia, as the current PALS bradycardia algorithm suggests.

Most of the studies were neutral with respect to the question. Angelos (LOE 5) evaluated ROSC in a rat model utilizing epinephrine vs placebo, and found that as the duration of cardiac arrest increased, epinephrine is more important to attain ROSC, but there was greater post-ROSC myocardial depression. Brady (LOE 5) was a study involving adult patients with hemodynamically compromising bradycardia or AVB with evidence of spontaneous circulation who received atropine delivered by EMS personnel, and in the hospital. 86 patients had bradycardia and approximately one-third of patients who received atropine in the prehospital setting for bradycardia had either a partial or complete response to therapy. The Chow study (LOE 5) was a histochemical and immunochemical analysis of the autonomic innervation of the human cardiac conduction system that demonstrated initial sympathetic dominance in infancy with gradual transition to sympathetic and parasympathetic innervation in adulthood. Kaplan (LOE 5) compared BG-9719, a selective A1AdoR antagonist to atropine or saline in a vagotomized, hypoxic rat model. Atropine and saline did not prolong survival or attenuate posthypoxic decreases in heart rate compared to BG-9719. McCaul (LOE 5) evaluated a brief asphyxial arrest rat model utilizing 10 or 30 mcg/kg of epinephrine vs saline, and demonstrated that epinephrine increased mortality, especially with the higher dose. The retrospective study by Iseri (LOE 5) evaluated adult patients in the prehospital setting in ventricular fibrillation or extreme bradycardia or asystole. Epinephrine or isoproterenol was given to 14 bradycardic patients, and atropine in 12 patients (either as treatment 1, 2 or 3), but results were inconsistent and only 1 patient survived to hospital day 12. Leinhart (LOE 4) was a case report on a 20 month old infant who suffered a near drowning. The first dose of epinephrine and atropine has no effect, but another dose of epinephrine and vasopressin resulted in ROSC.

There were only 2 studies that opposed the use of atropine. The Coon study (LOE 5) evaluated atropine after epinephrine (and other drugs). Twenty one prehospital adults who suffered cardiac arrest and were then in asystole or pulseless idioventricular rhythm (PIVR) were studied. There was no difference between the 2 groups (control n=11 and atropine (N=10) with respect to rhythm changes, pulse, admission or hospital discharge, so atropine did not improve outcome. The other study to oppose the use of atropine was a randomized study by Horigome (LOE1), which involved 21 prehospital adults in cardiac arrest, all whom were in asystole as the initial rhythm or as a result of defibrillation. Six failed to respond to epinephrine, but responded to atropine. And 50% of these patients were discharged from the hospital. In the prehospital study by Stueven (LOE 5), which was a retrospective review, there were 84 adult patients in asystole who remained in asystole after epinephrine (and sodium bicarbonate). Of these patients, 43 also received atropine, and 6 had successful resuscitation, which was defined as conveyance of a patient with a rhythm and pulse to an emergency department vs 0/41 of the epinephrine, sodium bicarbonate group, (P<.04). However, none of the patients who received atropine survived to hospital discharge. Therefore, this study is neutral with respect to survival to hospital discharge.
of a dose of 0.02 mg/kg over 0.01 mg/kg. While this does not answer the question about if epinephrine is better than atropine in bradycardia, it is known that epinephrine increases the heart rate and myocardial contractility, so it could be of more benefit in bradycardia unresponsive to oxygenation and ventilation.

Kurosawa: Some adult studies (Smith, Yilmaz, Brady, Chadda, all LOE 5) and a pediatrics study (Zimmerman LOE 4) indicated that iv atropine improved heart rate in symptomatic bradycardia. Atropine is effective for cardiac arrest or resuscitated symptomatic bradycardia. But it was not clear whether atropine was given during CPR in progress.

In a second NRCPR study, (Reis 2002) 129 pediatric patients who received cardiopulmonary resuscitation for cardiac arrest or symptomatic bradycardia were studied. The relative risk of death at 24 hours with resuscitation with atropine, after multivariate adjustment for potential confounders, was 1.2 (1.0-1.3). Stiell (LOE 5) reported a large observational cohort study of cardiac arrest in adult cases. 529 adult patients who suffered in-hospital and out-of-hospital cardiac arrest were studied. The odds ratio (95% CIs) for successful resuscitation with atropine, after multivariate adjustment for potential confounders, was 1.2 (1.0-1.3).

From the National Registry of Cardiopulmonary Resuscitation (NRCPR), Meany. (LOE 3) reported 464 pediatric ICU arrests The odds ratio (95% CIs) for survival to discharge with atropine was 2.38 (1.20-4.74) using multivariate logistic regression analysis. In a second NRCPR study, (Reis 2002) 129 pediatric patients who received cardiopulmonary resuscitation for cardiac arrest or symptomatic bradycardia were studied. The relative risk of death at 24 hours with atropine was 0.98 (0.58-1.90) using multivariate logistic regression analysis. These results suggest that atropine may be effective in cardiac arrest or resuscitated symptomatic bradycardia. But it was not clear whether atropine was given while CPR in progress.

There are one adult (Sorensen, LOE 5) and two pediatric case series (Fullerton, Thrush, both LOE 4), evaluating treatment of bradycardia presumed to be caused by vagal stimulation. Four cardiac surgical patients exhibited...
cardiovascular collapse in early postoperative course and were resuscitated. The vaso-vagal reflex was suspected and treated with atropine (Fullerton). Severe hypertension with reflex bradycardia progressed to cardiac arrest caused by drug and treated with atropine and cardiopulmonary resuscitation (Thrush). These studies support atropine use for pediatric in-hospital asystolic cardiac arrest or symptomatic bradycardia caused by increased vagal activity.

There are some studies which do not support the use of atropine. The Coon study is mentioned above. A prospective, controlled, blinded canine asphyxial PEA model; pediatric asphyxial cardiac arrest model was used by DeBehnke (1995). After 10 minutes untreated PEA, the animals were block randomized to one of five groups and each group was treated with different dose of atropine. The standard dose of atropine did not improve ROSC rate compared with control group. Increasing dose of atropine tended to decrease ROSC rates compared with control group and standard dose group.

Two cohort studies of out-of-cardiac arrest showed no evidence that treatment with atropine increase the chance of survival among asystolic patients (Engdahl, 2000) and cardiac arrest patients (Herlitz, 2003). Although these studies included pediatric patients in cardiac arrest, they were not separated in the analysis. In pediatric patients, hypoxemia, hypothermia, acidosis, hypotension, hypoglycemia, central nervous system insults and excessive vagal stimulation may produce symptomatic bradycardia and asystole. Asystole can be exacerbated by excessive vagal tone and the administration of atropine is reasonable for its physiological effects.

**Acknowledgements:**

**Citation List**

LOE 5, neutral. Animal (rat) study Quality of evidence good.
Sponsored by Roessler Scholarship Fund, Ohio State Univ, SAEM Institutional Training Award, Ohio State Initiatives Grant and The American Heart Association, Ohio Affiliate.

Comments: Level 5; good. Supportive

LOE 5, neutral. Adult population. Quality of evidence fair.
No industry funding.

LOE 5, atropine better than epinephrine. Adult study. Quality of evidence poor.
No industry funding.


No industry funding.
LOE 5: Controlled, prospective study in adults, neutral with respect to change in rhythm or survival.
No industry funding. Quality of evidence good

Comments: Level 5; Good. Opposing

Comments: Level 3; Poor. Opposing

LOE 4, Case series. Atropine better than epinephrine. Quality of evidence poor.
No industry funding


Comments: Level 3; Poor. Opposing

Comments: Level 3; Poor. Opposing

LOE 1, randomized, controlled study in children. Against the use of atropine to improve myocardial depression caused by halothane anesthesia. Quality of evidence good.
No industry funding

NHLBI funded

No industry funding

LOE 4, case series favors atropine. Quality of evidence poor.
No industry funding


Comments: Level 5; Fair. Supportive

LOE 5, Favors atropine. Adult study, retrospective review. Quality of evidence poor.

Comments: Level 4; Poor. Supportive


As a common causes of intraoperative bradycardia are hypoxia or vagal activity, such therapy should consist of ventilation with oxygen and iv atropine

Not used for LOE, as no studies found that met criteria
Ziino AJA, Davies MW, Davis PG. Epinephrine for the resuscitation of apparently stillborn or extremely bradycardia newborn infants. Cochrane Database of Systematic reviews 2008 (First published 2002, Issue 3 Art No: CD003849. Not used for LOE, as no studies found that met criteria.

Background
Epinephrine is a cardiac stimulant with complex effects on the heart and blood vessels. It has been used for decades in all age groups to treat cardiac arrest and bradycardia. Despite formal guidelines for the use of epinephrine in neonatal resuscitation, the evidence for these recommendations has not yet been rigorously scrutinised. While it is understood that this evidence is in large part derived from animal models and the adult human population, the contribution from work in the neonatal population remains unclear. In particular, it remains to be determined if any randomised studies in neonates have helped to establish if the administration of epinephrine in the context of apparent stillbirth or extreme bradycardia might influence mortality and morbidity.

Objectives
Primary objective:
To determine the effect of administration of epinephrine to apparently stillborn and extremely bradycardic newborns on mortality and morbidity
Secondary objectives:
To determine the effect of intravenous vs. endotracheal administration on mortality and morbidity
To determine the effect of high dose vs. standard dose epinephrine on mortality and morbidity (where high dose is defined as any dose greater than the current recommended standard dose of 0.1 to 0.3ml/kg of a 1:10,000 solution of epinephrine)
To determine whether the effect of epinephrine on mortality and morbidity varies with gestational age [i.e. term (greater than or equal to 37 weeks) versus preterm (less than 37 weeks)]

Search strategy
Searches were made of Medline from 1966 to August 2007, CINAHL (from 1982), Current Contents (from 1988), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007). Bibliographies of conference proceedings were reviewed and unpublished studies were sought by hand searching the
conference proceedings of the Society for Pediatric Research and the European Society for Pediatric Research from 1993 to 2007.

Selection criteria
Randomised and quasi-randomised controlled trials of newborns, both pre-term and term, receiving epinephrine for unexpected apparent stillbirth or extreme bradycardia.

Data collection and analysis
No studies were found meeting the criteria for inclusion in this review

Main results
No studies were found meeting the criteria for inclusion in this review.

Authors’ conclusions
No randomised, controlled trials evaluating the administration of epinephrine to the apparently stillborn or extremely bradycardic newborn infant were found. Similarly, no randomised, controlled trials that addressed the issues of optimum dosage and route of administration of epinephrine were found. Current recommendations for the use of epinephrine in newborn infants are based only on evidence derived from animal models and the human adult literature. Randomised trials in neonates are urgently required to determine the role of epinephrine in this population. No randomized controlled trials were found that support or refute that the administration of epinephrine to the apparently stillborn or extremely bradycardic newborn infant reduces mortality and morbidity.