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

**Worksheet author(s)**
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### Clinical question.

ALS-SC-073-9A: In adults with severe cardiovascular toxicity or life-threatening toxicity (prehospital or in-hospital) due to digoxin and related cardiac glycoside toxicity (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (e.g. ROSC, survival, neurologically-intact survival)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Yes - Intervention/therapy.

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

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### Conflict of interest specific to this question

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

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

PubMed “digoxin toxicity” or digoxin poisoning” or “cardiac glycoside poisoning” or “cardiac glycoside toxicity” or “plant poisoning” or “plant toxicity” as MESH (headings) AND “digibind” or “digoxin specific antibody” or “magnesium” or “lidocaine” or “antiarrhythmic.” EMBASE search using text words (all fields) digibind AND (digoxin toxicity OR cardiac glycoside toxicity OR plant poisoning).

AHA EndNote Master library, Cochrane database for systematic reviews, Central Register of Controlled Trials, Review of references from articles. Last Searched January, 2010.

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### State inclusion and exclusion criteria

**Inclusion criteria:** Controlled trials where antidotes were administered to patients with severe digoxin or cardiac glycoside toxicity in English language journals.

**Exclusion criteria:** Review articles, in-vivo studies and reports of single cases.

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### Number of articles/sources meeting criteria for further review

98 articles were identified by the search.

15 studies met criteria for further review. Of these one was LOE 1 (RCTs), 10 were LOE 4 (no controls), and four were LOE 5 (all animal studies).
# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Eddleston, 2000, 967. A</th>
<th>Smith, 1982, 1357. B*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td></td>
<td>Wenger, 1985, 118A. B*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antman, 1990, 1744. B*</td>
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<td></td>
<td></td>
<td>Wolf, 1992, 1739. B*</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>Hicke, 1991, 590. B^</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wolf, 1991, 16. B*^</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taboulet, 261. 1993 C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lapostolle, 2008, 3014. B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohen, 1983, 2808. A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(magnesium)</td>
</tr>
</tbody>
</table>

### Level of evidence

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>

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

* = overlapping patients group 1  
^ = overlapping patients group 2
# Evidence Neutral to Clinical Question

| Good | | | | | |
|------|------|------|------|------|
| Fair | | | | | |
| Poor | | | | | |
| 1    | 2    | 3    | 4    | 5    |

**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 Opposing Clinical Question

| Good | | | | | |
|------|------|------|------|------|
| Fair | | | | | |
| Poor | | | | | |
| 1    | 2    | 3    | 4    | 5    |

**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*
DISCUSSION: A number of interventions have been proposed for severe cardiovascular toxicity or life-threatening toxicity (prehospital or in-hospital) due to digoxin and related cardiac glycoside toxicity. These include digitalis specific Fab fragments, magnesium and antiarrhythmics. However, only a limited number of the studies met criteria for inclusion. Almost all of these studies involved digitalis specific Fab fragments (14 of 15 studies included).

Initial animal studies of severe digoxin toxicity are all supportive in the efficacy of digitalis specific Fab fragments. Additional animal models of other cardiac glycoside (toad venom, Chan Su and oleander) toxicity are also all supportive of Fab fragment efficacy.

Human studies of anti-digitalis Fab fragments for severe digitalis toxicity have been entirely observational in nature. However, all of the available studies have been supportive for the utility of this antidote.

The only human randomized controlled study involves cardiac glycoside toxicity due to oleander poisoning in Sri Lanka. Patients who had arrhythmias due to oleander toxicity were randomized to digitalis specific Fab fragment therapy versus placebo in a blinded fashion. The main endpoint was resolution of arrhythmia at 2 hours post therapy and return to normal sinus rhythm at 8 hours. Use of the Fab fragments was statistically significant in a beneficial fashion for both of these outcomes.

There appears to be good evidence supporting the use of digitalis specific Fab fragments for severe cardiac glycoside toxicity. Its use should occur in severe cardiac glycoside toxicity associated with arrhythmias. Its use in patients with cardiac glycoside toxicity in association with other poor prognostic signs such as increased age, increased potassium, underlying heart disease and cardiac shock is not well studied but may be useful.

Dosing of anti-digitalis Fab fragments for cardiac glycoside toxicity is not well studied. In the only randomized human controlled study (Eddleston, 2000, 967), a dose of 1200 mg of Fab fragments was utilized for toxicity due to oleander. Fab fragment dosing for severe digoxin toxicity based on observational study appears to suggest the use of equimolar dosing of Fab fragment with digoxin dose. However, human dosing studies for severe digoxin toxicity have not been performed.

With regards to other interventions for severe cardiovascular toxicity or life-threatening toxicity (prehospital or in-hospital) due to digoxin and related cardiac glycoside toxicity, the available data is limited and of low quality. A single LOE 4 study of poor methodologic quality (Cohen, 1983, 2808) was found to support the use of magnesium for idionodal tachycardia attributed to chronic digitalis toxicity.

Statistical summary of critical study: Eddleston, 2000, 967.
- 66 enrolled
- Arrhythmia resolution at 2 hours: 15/34 [44% in Dig Fab group] vs 2/32 [6% in placebo group] (RR 7.50, p < 0.001; Number Needed to Treat = 3).
- Normal sinus rhythm at 8 hours: 24/34 [71% in Dig Fab group] vs 5/32 [16% in placebo group] (RR 4.27, p < 0.001; Number Needed to Treat = 2)

Acknowledgements: Nil
Citation List


Level 4 study: prospective case series of severe digoxin or digotoxin toxicity without a control group. The methodologic quality is good and the study is supportive. 155 patients with severe life-threatening cardiac glycoside toxicity were treated with digoxin-specific antibody fragments. 80% had a complete response to therapy.

Two previously published papers reported interim results from this study: Smith TW, et al NEJM 1982; and Wenger TL, et al JACC 1985. Further, a subgroup analysis of pediatric patients from this pool of patients were separately reported (Wolf AD, et al. NEJM 1992). Further a compilation of several studies including published case reports include patients from this study (Wenger TL, et al. Amer J Emerg Med 1991; Wolf AD, et al. Amer J Emerg Med 1991). This report has overlap of reported patients with these five studies.


Level 5 (animals), supporting. Good (randomised control trial). A mouse model of Chan Su extract (cardiac glycoside from toad venom) toxicity. The main outcome was survival at 6 hours.


Level 5 (animals), supporting. Good (randomised control trial). A dog model of oleander (plant derived cardiac glycoside) toxicity. The main outcome was survival at 3 hours.


Level 4 study: a case series of seven patients with congestive heart failure and long term diuretic therapy with arrhythmias felt to be due to digitalis toxicity. All of the cases were treated with magnesium and were felt to have successful outcomes due to this therapy. The methodologic quality is poor and the study is supportive.


Level 1 study: This is a double blind placebo controlled study assessing the efficacy of anti-digoxin Fab fragments in patients with arrhythmias due oleander (plant derived cardiac glycoside) toxicity. The methodologic quality was good. 66 patients were randomized with 34 receiving study drug. At 2 hours post Fab administration 15 or 34 study drug recipients and 2 of 32 placebo patients had resolution of their arrhythmia. At 8 hours 24 of 24 study drug and 5 of 32 placebo patients were in normal sinus rhythm.


Level 4 study: this was a post marketing observational surveillance study. The methodologic quality is poor and the study is supportive.
717 patients who received digoxin-specific antibody fragments were reported on. All patient received the antibody fragments for treatment of suspected digitalis poisoning. 75% had a complete or partial response to therapy.


Level 5 (animals), supporting. Good (randomised control trial). A dog model of digoxin induced arrhythmias. The main outcome was resolution of arrhythmias.


Level 4 study: this was retrospective study of patients with digoxin toxicity that were treated with anti-digitalis Fab fragments. The methodologic quality is poor and the study is supportive. Patients who had cardiac glycoside toxicity but were not treated with Fab fragments and patients who received Fab fragments and cardiac pacing were excluded. 141 patient with digitalis poisoning were identified during the study period. 74 were excluded. Of patients included in the study 91% had a positive response after Fab fragment administration.


Level 5 (animals), supporting. Good (randomised control trial). A guinea pig model of digoxin toxicity. The main outcome was survival.


Level 4 study: prospective case series of severe digoxin or digotoxin toxicity without a control group. The methodologic quality is good and the study is supportive. 26 patients with severe life-threatening cardiac glycoside toxicity were treated with digoxin-specific antibody fragments. 21 if 23 had a favorable response to therapy. This paper reported on the initial results from this large multicenter study. There was a interim report (Wenger TL, et al. JACC 1985) and a final report (Antman EM, et al. Circ 1990) published. Further, a subgroup analysis of pediatric patients from this pool of patients were separately reported (Wolf AD, et al. NEJM 1992). Further a compilation of several studies including published case reports include patients from this study (Wenger TL, et al. Amer J Emerg Med 1991; Wolf AD, et al. Amer J Emerg Med 1991). This report has overlap of reported patients with these five studies.


Level 4 study: a retrospective case series of patients with digitalis toxicity comparing patients that were treated with digoxin-specific Fab fragments versus patients treated with pacing. The methodologic quality is poor and the study is supportive. The prevention of life-threatening arrhythmia was less in the group receiving Fab fragments.

Level 4 study: prospective case series of severe digoxin or digotoxin toxicity without a control group. The methodologic quality is good and the study is supportive. 63 patients with severe life-threatening cardiac glycoside toxicity were treated with digoxin-specific antibody fragments. 95% had a favorable response to therapy. One previously published paper reported on interim results from this large multicenter study (Smith TW, et al. NEJM 1982). A subsequent study reported on the final results from this study (Antman EM, et al. Circ 1990). Further, a subgroup analysis of pediatric patients from this pool of patients were separately reported (Wolf AD, et al. NEJM 1992). Further a compilation of several studies including published case reports include patients from this study (Wenger TL, et al. Amer J Emerg Med 1991; Wolf AD, et al. Amer J Emerg Med 1991). This report has overlap of reported patients with these five studies.


Level 4 study: prospective case series of severe pediatric digoxin or digotoxin toxicity without a control group. The methodologic quality is good and the study is supportive. 29 childrens with severe life-threatening cardiac glycoside toxicity were treated with digoxin-specific antibody fragments. 93% had resolution of toxicity after Fab administration. This study was a subgroup analysis of a large multicenter study that included adults. The results from the study were published in two interim analyses and a final report (Smith TW, et al. NEJM 1982; Wenger TL, et al. JACC 1985; and Antman EM, et al. Circ 1990). Further a compilation of several studies including published case reports include patients from this study (Wenger TL, et al. Amer J Emerg Med 1991; Wolf AD, et al. Amer J Emerg Med 1991). This report has overlap of reported patients with these five studies.