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Review

Antidote use for cardiac arrest or hemodynamic instability due to cardiac glycoside poisoning: A narrative review

Jessie Beaulieu[a,b,c], *Maude St-Onge*[a,c,d,e,*]

Abstract

Introduction: Cardiac glycosides comprise medications such as digoxin and digitoxin, plants, and even certain toad venoms. Intoxication with cardiac glycosides can lead to hemodynamic instability and cardiac arrest. With this narrative review, our objective was to determine if any therapy used in a near-cardiac arrest state due to cardiac glycoside poisoning could improve survival with favourable functional and neurological outcomes.

Methods: We searched the Medline, PubMed, EMBASE and Cochrane Library databases up to February 2022 for controlled trials, observational studies, and case reports. We reviewed studies if participants were exposed to a cardiac glycoside, had hemodynamic instability, and an intervention was attempted to reverse the toxicity. The effect of interventions on (1) survival with favourable functional and neurological outcomes and (2) correction of hemodynamic instability was assessed.

Results: Of the 2422 studies found, 73 were included for analysis, of which 58 were case reports or series, and 15 were observational cohorts. Most patients were intoxicated with medication (60 individual cases and 11 observational cohorts). Administration of digoxin immune-Fab fragments was associated with improved hemodynamic status and survival in medication patients. Administration of magnesium, cardioversion, and cardiac pacing was associated with favourable outcomes, while administration of atropine, antiarrhythmics, or calcium was not.

Conclusion: In patients with hemodynamic instability due to cardiac glycoside intoxication, digoxin immune-Fab fragments should be given, and magnesium administration, cardioversion, and cardiac pacing can reasonably be attempted.

Keywords: Cardiac glycoside intoxication, Digoxin intoxication, Resuscitation, Cardiac arrest

Introduction

Cardiac glycosides comprise medications, plants, and even certain toad venoms. Even with their fading use for chronic cardiopathies and arrhythmias, cardiac glycoside medications remain a significant cause of poisoning because of their narrow therapeutic range, pharmacological interactions, and renal elimination.[1] In the United States in 2020, 1498 cases of cardiac glycoside medication intoxication were reported, of which 526 were moderate-to-severe, and 28 caused death.[2] In the same year, 2050 exposures to cardiac glycoside from plants were recorded.[2] Cardiac glycoside toxicity causes gastrointestinal manifestations, confusion, weakness, and, more importantly, various cardiac conduction abnormalities leading to severe arrhythmias, cardiac arrest, and death.[3–5] Management of such poisonings includes decontamination with activated charcoal,[6–9] supportive care, and correction of electrolyte disorders.[10–11] However, when patients are unstable or in cardiac arrest, these treatment options are insufficient, and antidotes are needed.

In 1976, Smith et al. described the reversal of digoxin toxicity with ovine digoxin immune-Fab fragments,[12] leading the path to immune therapy currently recommended by experts in severe cardiac glycoside medication poisoning.[1,13] A systematic review in 2014[1] compiled the kinetics of digoxin immune-Fab fragments to understand better the dose required. While most patients appear to have a good clinical response to digoxin immune-Fab fragments, the extent to which hemodynamically unstable patients benefit from it remains unclear. This effect appears the same for patients intoxicated with plants containing cardiac glycoside, but the evidence is scarce.[5] The Extracorporeal Treatments In Poisoning Workgroup concluded

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in 2016 that extracorporeal treatments (dialysis and hemoperfusion) should not be used in digoxin poisoning for poison removal, even with hemodynamic instability,[4] because of limited dialyzability.

Therefore, it is currently unclear which therapy should be prioritized for a cardiac glycoside-intoxicated patient in a near cardiac arrest state. With this narrative review, our objective was to determine if any therapy used in these situations, adjunct to standard resuscitation, could improve survival with favourable functional and neurological outcomes. We also aimed at describing treatment strategies associated with improvement in hemodynamic parameters and return of spontaneous circulation.

Methods

Eligibility criteria

Study types

All study designs were considered, including controlled trials, observational studies, case series, and case reports, without any date restriction. We distinguished case series from observational cohorts using the approach of Dekkers et al.[14] Animal studies, in-vitro studies, book chapters, editorials, commentaries, and other systematic and non-systematic reviews were excluded. Studies in languages other than English or French were excluded.

Participants

Studies were eligible if they involved humans intoxicated with a cardiac glycoside. Intoxication was defined as exposure to a cardiac glycoside, intentional or not, capable of causing clinical toxicity. Intoxications with *Taxus* sp. were excluded since cardiac glycoside toxicity does not appear to be its primary toxicity mechanism. We included patients with polyintoxication. Patients had to have hemodynamic instability, defined by life-threatening arrhythmia (ventricular arrhythmia, bradycardia <50 bpm, or complete atrioventricular [AV] block), systemic hypotension (<90 mmHg systolic or < 65 mmHg mean arterial pressure), respiratory failure, or cardiac arrest. Patients were also included if the author mentioned life-threatening arrhythmia, shock, hypotension, or cardiac arrest without providing the vital signs. Case series involving one or more patients meeting the criteria were included, and data from the pertinent cases were extracted, while other cases were not included in this review.

Interventions

Any intervention meant to improve the outcome was considered eligible. We excluded studies about decontamination (activated charcoal, total intestinal irrigation, or gastric lavage) since these interventions cannot be given during cardiac arrest. We excluded studies if no intervention was made to reverse the toxicity.

Outcome measures

Studies had to document at least one outcome of interest. The primary outcome was survival with favourable functional and neurological outcomes. The secondary outcomes were the return of spontaneous circulation and the correction of hemodynamic parameters. The latter was defined as improvements in heart rate, blood pressure, or breathing pattern. If no information could be found on the intervention's effect, it was considered not to have improved hemodynamic status.

Data collection

We collected information about the ingested cardiac glycoside, the measured serum medication levels, and the timing of the intoxication. We considered the intoxication acute if massive ingestion was reported, regardless of whether the patient was chronically taking cardiac glycoside medication. A non-intentional accumulation of medication was considered chronic, as was the initiation of medication at a supra-therapeutic dosage. We extracted the interventions used, their short-term effect, and the patient's outcome at discharge.

Search strategy

We searched the Ovid/Medline, PubMed, EMBASE, and Cochrane Library databases up to February 2022 without time restriction. The research strategy can be found in the *Supplementary Material*. Two independent reviewers (JB and MSO) selected the studies based on inclusion and exclusion criteria. Discrepancies were resolved by consensus and involved a third reviewer when required. Qualitative synthesis was used to summarize the evidence for each outcome.

Results

After removing duplicates, 2422 studies were found, of which 265 were assessed by full-text review. We subsequently included 73 studies in this narrative review. The reasons for exclusion are presented in Fig. 1. No randomized study was found. We found 58 case reports or series,[15–72] totalling 83 patients meeting the inclusion criteria. Among the cases, 60 were intoxicated with cardiac glycoside medication and 23 with another cardiac glycoside: six with *Nerium oleander* or *Thevetia peruviana* (oleander and yellow oleander), nine with *Bufo* toad venom, three with *Digitalis purpurea* (foxglove), three with *Cerbera odollam* (pong-pong seeds, in the same case series), and two with coconut crab contaminated with *Cerbera manghas* (in the same case series). Overall, 58 of our 83 cases survived with a favourable outcome (70%), including 48 patients intoxicated with medication (80%) and 10 patients (43%) with other cardiac glycosides. Fifty acutely ingested the agent, while 31 had a chronic intoxication pattern. The timing of ingestion was unclear in two cases. Seven cases had a polyintoxication, of which six were acute ingestions. Many cases received more than one intervention. A complete description of these interventions can be found in Figs. 2 and 3 and Tables 1 and 2.

We also reviewed 15 cohorts or case series without case-level data meeting our criteria.[73–87] Eleven of these 15 cohorts or case series included patients intoxicated with medication, three focused on populations intoxicated with *Thevetia peruviana* (yellow oleander), and one focused on *Bufo* toad venom. These cohorts are described in Table 3.

Digoxin-immune Fab fragments

Cardiac glycoside medication

This intervention was studied in many cohorts[73,76,80,83–85] showing a significant improvement in hemodynamic status for life-threatening intoxications treated with digoxin-immune Fab fragments. No comparative group in these cohorts allowed us to show a survival benefit.

Among the cases reports and series, 22/24 cases reported an improvement in hemodynamic status after administration of

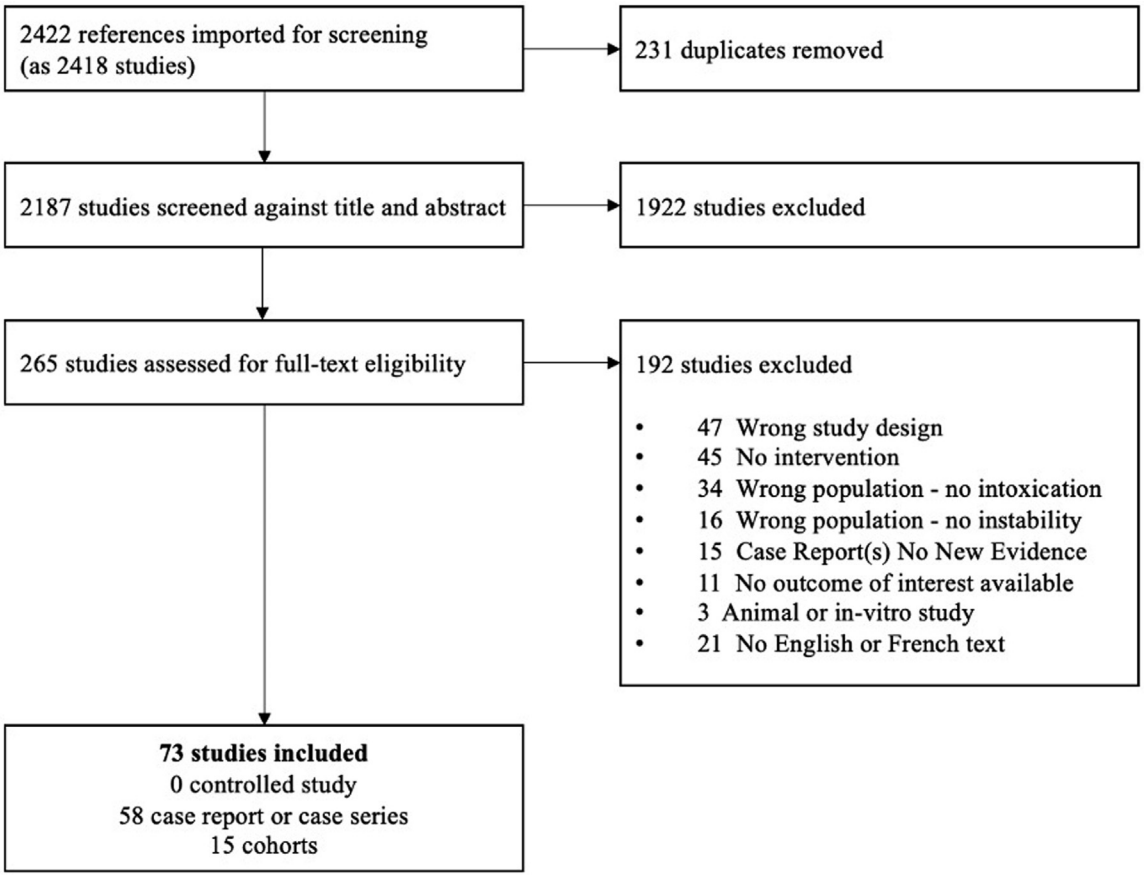

Fig. 1 – PRISMA flowchart. Made with CMap Tools.

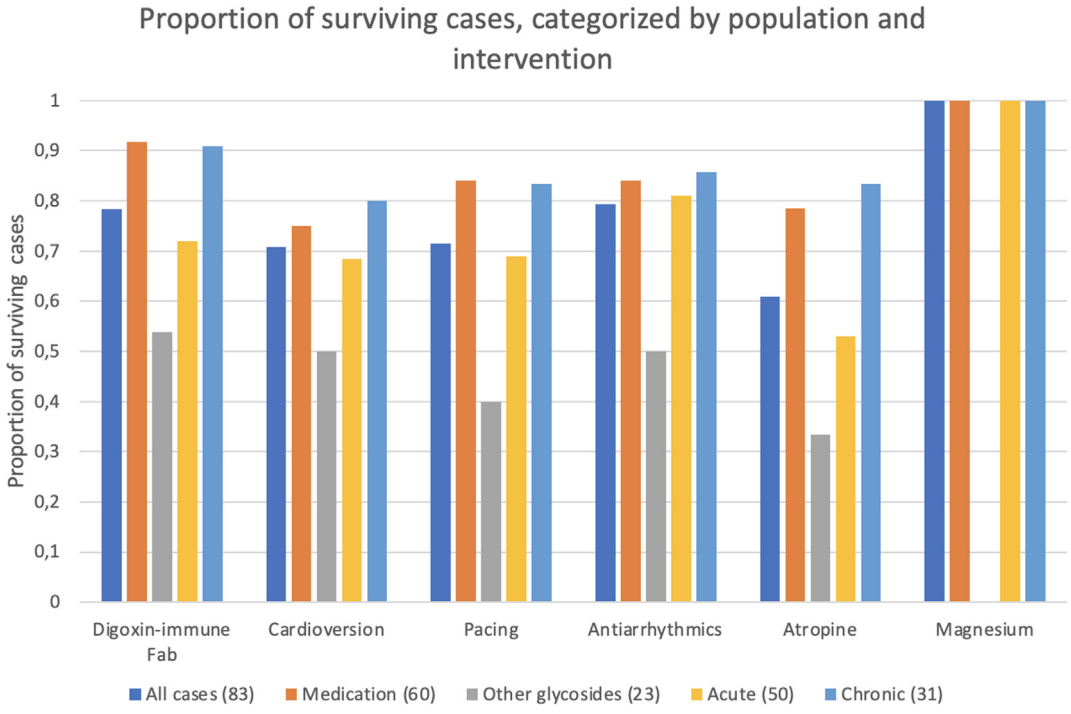

Fig. 2 – Proportion of surviving cases, categorized by population and intervention. Made with Powerpoint.

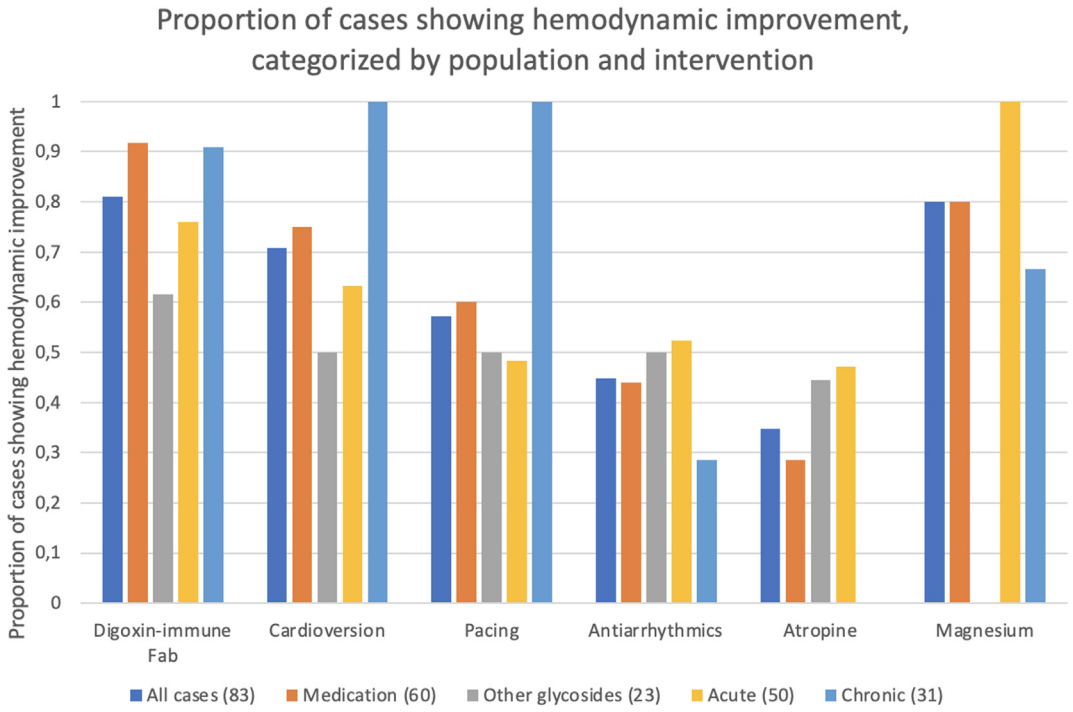

Fig. 3 – Proportion of cases showing hemodynamic improvement, categorized by population and intervention. Made with Powerpoint.

Table 1 – Intervention resulting in survival and transient or sustained improvement in hemodynamic status in individual cases by substance.

Intervention	Total cases (*n* = 83), HD improvement	Total cases (*n* = 83), survival	Medication (*n* = 60), HD improvement	Medication (*n* = 60), survival	Other glycosides (*n* = 23), HD improvement	Other glycosides (*n* = 23), survival
Digoxin-immune Fab fragments	30/37	29/37	22/24	22/24	8/13	7/13
Cardioversion	17/24	17/24	15/20	15/20	2/4	2/4
Pacing	20/35	25/35	15/25	21/25	5/10	4/10
Antiarrhythmic medication	13/29	23/29	11/25	21/25	2/4	2/4
Atropine	8/23	14/23	4/14	11/14	4/9	3/9
Magnesium	4/5	5/5	4/5	5/5	0/0	0/0

Reported as x/y, where x is the number of favourable outcomes, and y is the total number of cases receiving the intervention in the population. Key: HD, hemodynamic.

digoxin-immune Fab fragments, and 22/24 survived. When excluding pediatric cases, 13/20 cases reported the digoxin-immune Fab fragments dose administered, and the mean dose was 13 vials of 40 mg, with a median of 10 vials. Their favourable outcome was consistent with the results described in the cohorts, with most patients showing a marked favourable evolution. The effect was even more convincing in chronic cases (10/11 improved, 10/11 survival). Most reported deaths with acute ingestions were patients who presented with severe hemodynamic collapse and prolonged low cardiac output state before digoxin-immune Fab fragments administration and then developed multi-organ failure. Among patients in cardiac arrest secondary to medication poisoning who received digoxin-immune Fab fragments, 6/7 had a return of spontaneous circulation.

Other cardiac glycosides

Eight out of 13 cases showed hemodynamic improvement, and 7/13 survived. However, the effect does not appear consistent for all causal agents. Cases intoxicated with oleander or yellow oleander appeared to have a good response. *Bufo* toad venom-intoxicated patients also appeared to show improvement with digoxin immune-Fab fragments administration before or shortly after cardiac arrest. While only three cases in one publication were found, intoxication with *Cerbera odollam* did not appear to respond to Fab fragments. The cases intoxicated with other cardiac glycosides received a median dose of 10 vials of 40 mg of digoxin-immune Fab fragments (11/13 reported the given dose, with a mean of nine vials).

Table 2 – Intervention resulting in survival and transient or sustained improvement in hemodynamic status in individual cases by intoxication timing.

Intervention	Total cases (n = 83), HD improvement	Total cases (n = 83), survival	Acute (n = 50), HD improvement	Acute (n = 50), survival	Chronic (n = 31), HD improvement	Chronic (n = 31), survival
Digoxin-immune Fab fragments	30/37	29/37	19/25	18/25	10/11	10/11
Cardioversion	17/24	17/24	12/19	13/19	5/5	4/5
Pacing	20/35	25/35	14/29	20/29	6/6	5/6
Antiarrhythmic medication	13/29	23/29	11/21	17/21	2/7	6/7
Atropine	8/23	14/23	8/17	9/17	0/6	5/6
Magnesium	4/5	5/5	2/2	2/2	2/3	3/3

Reported as x/y, where x is the number of favourable outcomes, and y is the total number of cases receiving the intervention in the population. Key: HD, hemodynamic.

Cardioversion

Cardioversion resulted in a hemodynamic improvement in 17/24 cases. Most non-responders did not change their rhythm when receiving cardioversion. However, some cases report a deterioration, namely the conversion of ventricular tachycardia (VT) or fibrillation (VF) without a pulse to asystolia.[34,46,56] Seventeen out of 24 patients survived, resembling the overall survival of all included cases. No cohort reported thoroughly the outcome of cardioversion.

Endovenous or transcutaneous pacing

The most evidence came from a 1976–1977 French cohort.[77,88] Those studies found an improvement in the same centre from a historical mortality rate of 20% to 13% when inserting endovenous pacemakers in high-risk digitoxin-intoxicated patients. Many complications of the technique were observed, more likely related to the novelty of the device and the lack of technical expertise. No digoxin-immune Fab fragments were available in that period. In our cases, 20/35 patients showed at least temporary improvement. However, some studies reported an inability to resume pacing when interrupted,[30,32,56,57,71,77] suggesting the precarity of the strategy. In more recent studies, it appeared to be more often used in other cardiac glycoside poisonings, as seen in the descriptive cohorts on yellow oleander. However, the outcomes of this specific intervention were not detailed.

Antiarrhythmic medication

Two cohorts reported successfully using antiarrhythmic therapy in patients intoxicated with digitalis or digoxin, one with diphenylhydantoin and one with lidocaine. The included patients had arrhythmias but no hemodynamic repercussions from them. In the cohort treated with diphenylhydantoin, serum levels were not available to prove the intoxication.

In the cases, sodium-channel blockers were mainly seen, namely lidocaine, phenytoin, diphenylhydantoin, and procainamide. Three cases reported the successful use of amiodarone,[22,53,57] and three reported the successful use of bretylium.[35,66] Less than half of the patients showed improvement from any antiarrhythmic therapy.

Atropine

Less than half of our cases (8/23) responded to atropine, while 13 survived. It was a frequently reported intervention in the cohorts, especially for patients poisoned with other cardiac glycosides. We could not ascertain the impact of atropine on patients' hemodynamic status in those cohorts because they were designed to describe the consequences of the intoxication rather than the impact of interventions. The number of treated patients and their outcomes was not reported.

Magnesium

In the reported cases, magnesium was not often attempted; only five patients received it. It improved almost all reported patients; four improved hemodynamically, and five survived. Because of the small number of reported cases, it is difficult to be certain about the effect of this intervention.

Potassium

Some cases showed an improvement after potassium administration, mainly in the context of chronic intoxication in patients who were also hypokalemic because of concurrent diuretic therapy.[21,27,33,43–44] Many of those cases were patients treated with digitalis-containing medication in the years before serum level measurements were readily available.

Calcium

Nine cases received calcium[23,43,54,60,62,64,69,71] to treat hyperkalemia. All but one died, and none showed an improvement in their hemodynamics. No asystolia or deterioration consequent to the treatment was reported, but those cases were severely unstable: five were in cardiac arrest at presentation or shortly after.

Other therapies (including extracorporeal epuration and circulation)

Ten cases reported using isoproterenol,[17,20,25,38,41,51,55,56,60] with only one showing short-term improvement in hemodynamic status and seven survivals. Two cases reported extracorporeal circulation,[19,71] with successful stabilization of hemodynamic status but subsequent death from complications. Nine cases attempted various extracorporeal epuration techniques (hemoperfusion, plasma exchange, hemodialysis, or hemofiltration).[45,54,55,61,65,66,69,71] The critical approach of clearance calculations for those techniques is beyond the scope of this review and has been previously addressed.[4] However, none of the articles reported complete data to calculate exact clearance.[89]

Table 3 – Description of cohort studies.

Study	Patients number	Population	Intervention	Outcome	STROBE
Digoxin, digitoxin or digitalis					
Bashour (1968)[75] Case series	12	Presumed chronically intoxicated with digitalis, but no dosage available and no intake history.VT and AF were mostly well tolerated.	Diphenylhydantoin	Most arrhythmias reversed with diphenylhydantoin, especially VT. No effect on atrial fibrillation. All patients had favourable outcomes, but details are missing.	2/22
Bismuth (1977)[77]Gaultier (1976)[88] Retrospective cohort	124(68 had a pacemaker)	Acute intoxications with digitoxin.If unstable or considered high-risk due to ingested dose, demographics, or kalemia, a pacemaker was inserted.	Endovenous pacemaker	23% of deaths among those receiving pacemakers (13% of all patients), better than the historical cohort in the same hospital.Many complications: accidental disconnection, breakdown of the pulse generating system, low pacing threshold, electrode displacement, and ventricular perforation.Deaths related to heart failure (2), VF (11), or sepsis (1) .	10/22
Castellanos (1982)[78] Retrospective cohort	9	Intoxicated with digoxin, timing unclear. Presenting with VT, mostly without hemodynamic impact.	Lidocaine, bolus followed by perfusion	One resolved by bolus only, four temporary improvements. All had improvement with perfusion; some recurred at the end of perfusion or in the hours after.All patients had favourable outcomes.	4/22
Antman (1990)[73] Retrospective cohort	150	50% chronic or acute-to-chronic intoxication, 50% acute. 93% digoxin, the remainder digitoxin or unspecified. 26% had cardiac arrest. 46% had refractory VT. 33% had VF. 53% had high-grade AV block.	Fab fragments 48% had a pacemaker 21% had cardioversion 54% had antiarrhythmics 22% had atropine 11% had a calcium channel blocker or beta-blocker	80% had a resolution of hemodynamic instability after the first Fab dose, 10% improved, and 10% had no effect. 71% survived to discharge. Of 43 deaths, 11 had no response to Fab. Of 56 patients in near cardiac arrest, 54% survived hospitalization.Those who did not respond were mostly not intoxicated with digoxin or had another explanation for symptoms except one.	14/22
Arbabian (2018)[74] Retrospective cohort	47(21 treated)	Digoxin, all chronic intoxications with bradycardia. Most had no hemodynamic impact.Most with calcium channel blocker, beta-blocker, and diuretics chronic use.	Fab fragments	Modest improvement of heart rate in the treated group compared to the untreated group, which was nonsignificant. No difference in mortality or hospital stay length.The treated group had more severe manifestations (indication bias) .	19/22
Bilbault (2009)[76] Retrospective cohort	20	Four acute and 16 chronic intoxications with digoxin with various arrhythmias, most unstable.	Two-step administration of Fab, with two vials (160 mg) and reassessment before another 160 mg.	70% recovered with the first step; 5/6 patients recovered with the second step. Global mortality was 15%. One patient died of refractory bradycardia, and two from other unrelated causes (heart failure and sepsis).	16/22

Table 3 (continued)

Study	Patients number	Population	Intervention	Outcome	STROBE
Chan (2019)[79] Prospective cohort	128(50 receiving Fab)	Chronically intoxicated with digoxin.No instability.	Fab, given before instability.	No difference in heart rate.No difference in mortality.One death in the control group; no other fatality related to the intoxication.	18/22
Lapostolle (2008)[80] Retrospective cohort	66	50% digoxin, 50% digitoxin. 73% had acute ingestions21 had life-threatening VT or bradycardia.	Fab, given before instability (prophylactically) or curatively.	All patients improved after treatment; 11 needed a second dose of Fab fragments. 7.6% mortality, of which all patients had a potential other cause for death or for initial arrhythmia.	16/22
Schaeffer (2010)[83] Retrospective cohort	14	Chronic intoxication with digoxin. All patients had life-threatening cardiac arrhythmia or cardiac arrest.	Fab fragments	13 patients improved after treatment. One patient did not improve but had another terminal disease and was oriented in hospice care. Another death was unrelated to intoxication (sepsis).	19/22
Smith (1982)[84] Retrospective cohort	23	20 digoxin, three digitoxin. All were chronically treated, but 16 were massive ingestions. 20 had refractory VT. Nine had VF. 19 had high-grade AV blocks. Four had prolonged low cardiac output states.	FabMany received antiarrhythmics, a pacemaker, and atropine and failed to respond.	18 had marked improvement. Four patients were treated after prolonged shock: all died of complications. One patient did not receive Fab when needed (because it was unavailable) and died. All others survived with favourable outcomes.	9/22
Smolarz (1985)[85] Retrospective cohort	34	31 digoxin, three digitoxin. 30 were acute, four were chronic. 18 had high-grade AV blocks. Eight had VF. Four had VT.12 had premature ventricular beats.	Fab fragments	32 improved during treatment. Two deaths, one from sepsis eight days later and one from cardiogenic shock because of an underlying condition. All others fully recovered.	7/22
Other cardiac glycosides					
Pirasath (2013)[81] Retrospective cohort	65	Acute poisonings with yellow oleander. 15% with no instability. 18% were life-threatening.	29 received atropine. 29 received isoproterenol.One had an endovenous pacemaker.	Descriptive cohort. Two deaths before the beginning of interventions, unstable VF. 83% of patients required intervention, and all survived.	9/22
Saraswat (1992)[82] Retrospective cohort	13	Acute poisonings with yellow oleander.	Atropine.Number of patients treated, dose and effect are not described.	Descriptive cohort to identify bad prognosis. Patients were divided into three groups depending on the amount ingested. Two patients died; one arrived >6 h after ingestion, the other had the highest ingested dose, presented more than 5 h after ingestion and “could not be revived due to shock.”	6/22
Zamani (2010)[87] Retrospective cohort	21	Acute poisonings with yellow oleander. 61% had electrocardiogram changes: VT or AV block.	Some had pacemakers, some had cardioversion.	Descriptive cohort, aiming to describe the cardiac effects of intoxication more than the effect of interventions.	5/22
Trakulsrichai (2020)[86] Retrospective cohort	36	Acute poisonings with *Bufo* toad venom. 12 with bradycardia. Seven with shock.One with cardiac arrest.	Seven had atropine One had endovenous pacingOne had Fab	Descriptive cohort. Mortality was 8.3%, and 75% were hospitalized with a mean stay of two days. Two patients subsequently developed cardiac arrest in the hospital.The one patient with endovenous pacing and Fab had a favourable outcome.	15/22

Discussion

Many interventions can be tried in patients with cardiac arrest, ventricular arrhythmias, severe bradycardia, and/or hemodynamic instability secondary to cardiac glycoside poisoning, including administration of digoxin-immune Fab fragments or antiarrhythmics, correction of electrolytes, cardioversion, or pacing. We found the highest number of studies were about administration of digoxin-immune Fab fragments to patients intoxicated with medication; all other interventions had limited literature to support them.. The most convincing effect was observed with digoxin-immune Fab fragments, with 92% of medication-poisoned patients showing hemodynamic improvement (30/37) and/or survival (29/37). The effect of digoxin-immune Fab fragments in intoxication with other cardiac glycosides remains unclear and variable depending on the exact ingested poison.

A 2014 systematic review by Chan et al.[1] found that response rates to digoxin-immune Fab fragments in the published cohorts varied from 50% to 80%–90% with a 30–45 min delay in both acute and chronic intoxication. These rates are consistent with our results for both the cohorts and cases (82% hemodynamic improvement and 76% survival in those receiving digoxin-immune Fab fragments), especially when considering only medication-intoxicated patients (92% survival and hemodynamic improvement). This finding suggests that digoxin-immune Fab fragment administration is effective even in the sickest patients. Evidence for poisonings with other cardiac glycosides is less clear and varies depending on the specific poison. Our *Nerium oleander* and *Thevetia peruviana* cases responded better than our *Cerbera* sp. cases, consistent with a randomized trial including stable patients intoxicated with yellow oleander published in 2000[90] who showed improved heart rate after administration of digoxin-immune Fab fragments. *Bufo* toad venom intoxication, also known as Chan-Su, also appears to have a good response rate to digoxin-immune Fab fragments administered before or shortly after cardiac arrest. In-vitro studies[93,94] support the reaction between the poison and the antidote. Considering that cardiac glycosides are varied and multiple, it is natural to hypothesize that some do not show adequate binding sites for digoxin-immune Fab fragments.

The dose of digoxin-immune Fab fragments required to reverse toxicity is currently unknown. Historically, the total body burden of digitalis was calculated, and digoxin-immune Fab fragments were prescribed accordingly, using a serum level drawn precisely six hours after the ingestion.[73,84] However, a recent systematic review and pharmacokinetic analysis of digoxin-immune Fab fragments in acute and chronic poisonings[1] concluded that 1–2 vials (40 to 80 mg) might be sufficient to reverse the effect of digitalis in the central compartment, with subsequent doses required if toxicity recurs. However, because of the small number of patients with imminent cardiac arrest, they could not recommend a specific dose for this specific population and conservatively suggested administering the full neutralizing dose. Our narrative review was not designed to answer that specific question, and it remains a critical research need.

In the 1980s, animal data raised concerns about defibrillation, cardioversion, and pacing in digitalis-poisoned patients, dreading the appearance of new life-threatening arrhythmias.[95] In our review, most patients (71%) showed at least a temporary improvement after cardioversion, with the remainder not responding to therapy. However, some patients converted from a shockable rhythm (VF or VT) to asystolia with attempted cardioversion. We do not believe that fear of asystolia should restrain physicians from cardioverting digoxin-poisoned patients in cardiac arrest or hemodynamic collapse due to a shockable rhythm since they are more likely to benefit from the intervention and are already being actively resuscitated. However, further consideration should be given when facing a stable digoxin-poisoned patient with VT. We did not find cases reporting arrhythmias triggered by pacing. However, it is challenging to discriminate between arrhythmias occurring in the natural history of the intoxication and those provoked by interventions.

We found that cases receiving calcium had a very poor prognosis, with only 1/9 surviving. However, those cases had a very unstable presentation and marked hyperkalemia, which was the reason they received calcium in the first place. There is uncertainty on the causal association between calcium administration and outcome, knowing that severely poisoned patients will present with arrhythmia, hyperkalemia, and worse outcomes with or without intervention.[11] Animal case reports from the 1930s[94,95] suggested intravenous calcium administration could harm. However, a recent retrospective cohort including mainly chronic poisonings[96] suggested otherwise, with no worsening of outcomes or arrhythmias. While there is no rationale for treating cardiac glycoside-intoxicated patients with intravenous calcium, evidence suggests it is not as dangerous as previously thought.

Our narrative review had many limitations, the greatest being the poor quality of publications and the limited number of published cases. Many case reports and cohorts reported incomplete data. Moreover, those publications often were prone to inherent bias. External validity is restricted for multiple reasons. First, most publications in which patients did not receive digoxin-immune Fab fragments were written before 1980 and therefore had different treatment strategies and experiences that might not represent the reality of current practice. Published cohorts using endovenous pacing and reporting a much higher rate of complications than expected are a good example. Second, it is difficult to discriminate the effect of a single intervention among many given to a single patient. Third, because patients now often receive digoxin-immune Fab fragments, it may influence the effect of other treatments (e.g., pacing and cardioversion). Fourth, we may not have identified all pertinent publications on intoxications with other cardiac glycosides. Finally, given the instability of our target population, some interventions could be justified even if there is a poor response rate.

Digoxin immune-Fab fragments should be given to patients with hemodynamic instability due to cardiac glycoside intoxication, and magnesium administration, cardioversion, and cardiac pacing can reasonably be attempted. Atropine, antiarrhythmics, or calcium administration was not associated with favourable outcomes. Further research is needed to characterize the effect of these interventions on the outcomes of severely poisoned patients and to clarify the appropriate digoxin immune-Fab fragments dose in these circumstances.

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CRediT authorship contribution statement

Jessie Beaulieu: Writing – original draft, Visualization, Validation, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Maude St-Onge:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [This work was done in parallel of the development of the 2023 guidelines of the American Heart Association.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100690.

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