REVIEW

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Expert Consensus on the Diagnosis and Management of Digoxin Toxicity

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ABSTRACT

While there has been a decline in the use of digoxin in patients with heart failure and atrial fibrillation, acute and chronic digoxin toxicity remains a significant clinical problem. Digoxin's narrow therapeutic window and nonspecific signs and symptoms of toxicity create clinical challenges and uncertainty around the diagnostic criteria of toxicity and responsive treatment choices for the bedside clinician. A systematic review of published literature on digoxin toxicity (34,587 publications over 6 decades, with 114 meeting inclusion criteria) was performed to develop 33 consensus statements on diagnostic and therapeutic approaches which were then evaluated through a modified Delphi process involving a panel of experts in cardiology, nursing, emergency medicine, and medical toxicology. The results demonstrate agreement about the need to consider time of ingestion and nature of the exposure (ie, acute, acute-on-chronic, chronic) and the use of digoxin immune Fab for life-threatening exposure to decrease risk of death. While several areas of continued uncertainty were identified, this work offers formalized guidance that may help providers better manage this persistent clinical challenge.

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KEYWORDS: Digoxin immune Fab; Digoxin toxicity; Expert consensus

INTRODUCTION

The role of digoxin in contemporary treatment algorithms for heart failure and atrial fibrillation has narrowed over time, but while overall use has declined,[1,2] the number of prescriptions (>1.5 million in 2021) and incidence of toxicity, including arrhythmia and death, remain significant.[3-6] Given the persistent use of digoxin in clinical practice, often in high-risk populations, its narrow therapeutic window, and the nonspecific nature of many signs and symptoms of toxicity, there is a continued critical need for clinicians to recognize and manage digoxin excess. For both life-threatening and non–life-threatening presentations of toxicity, management options are limited and, with the exception of the administration of digoxin immune Fab, are associated with uncertain efficacy. Further, the threshold and indications for digoxin immune Fab treatment remain clinically uncertain, in part due to cost considerations, lack of data from randomized double-blind, placebo-controlled trials, and relatively modest trends toward decreased mortality.[6,7] Additionally,

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despite the morbidity and mortality associated with digoxin toxicity, data suggest that it is often unrecognized, and management is inconsistent.[8]

We performed an exhaustive formal systematic review of published and grey literature (systematic literature review [SLR]) involving digoxin toxicity (presentation, diagnosis, and treatment) and engaged a panel of experts who have published in the field from cardiology, nursing, emergency medicine, and medical toxicology. The panel developed consensus statements about digoxin toxicity, including diagnostic and therapeutic approaches, based on the SLR and using a formal modified Delphi process.

CLINICAL SIGNIFICANCE

- Assessment of digoxin toxicity should consider the patient's age, renal function, nature of exposure, time of ingestion, serum digoxin level, and serum potassium level.
- Because symptoms of digoxin toxicity may be nonspecific, the clinical context is important in determining the threshold for administration of digoxin immune Fab.
- Digoxin immune Fab is recommended in the setting of potentially life-threatening digoxin exposure to decrease risk of death.

METHODS

This project used an SLR and modified Delphi process (Figure 1) that involved a series of surveys. Participants included 3 Steering Committee (SC) members and 11 panelists from various medical fields (Table S1). The SLR and modified Delphi analysis did not require review by an ethics review committee. All data collection procedures and key terms (Table 1) were defined a priori, and the authors were not blinded to the authors, journals, or funding sources noted in the SLR. Panelists responded to surveys via online methodology, and responses were anonymized.

A pre-SLR survey (Survey 1) was undertaken to explore and define the key clinical parameters related to diagnosis and management of patients with digoxin toxicity upon which the SLR would be based. To prepare for Survey 1, SC members developed open-ended statements and statements with multiple choice options related to these parameters. Panelists responded to 14 questions on a 5-point Likert scale (options ranging from 1 = "Definitely No" to 5 = "Definitely Yes", with an option for "I Don't Know") with space provided for open-text comments.

An SLR was then conducted to obtain published evidence about the key topics of interest that were deemed relevant based on the results of Survey 1. The strategies for the SLR, conducted in accordance with PRISMA guidelines,[9] included establishing the Population, Intervention, Comparison, and Outcomes (PICO) criteria, selecting time frames, countries of origin and databases, and choosing search terms and parameters (Tables S2 and S3). All search results were entered into the Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia) SLR management platform and deduplicated. Title, abstract, and full text screening for relevance were performed independently by 2 SC members, with a third member adjudicating any disagreements.

Data from the publications that met criteria were extracted by 2 authors using a standardized spreadsheet with items based on the responses to Survey 1. The SLR results informed the development of draft statements and the level of evidence for each, graded by the same 2 authors

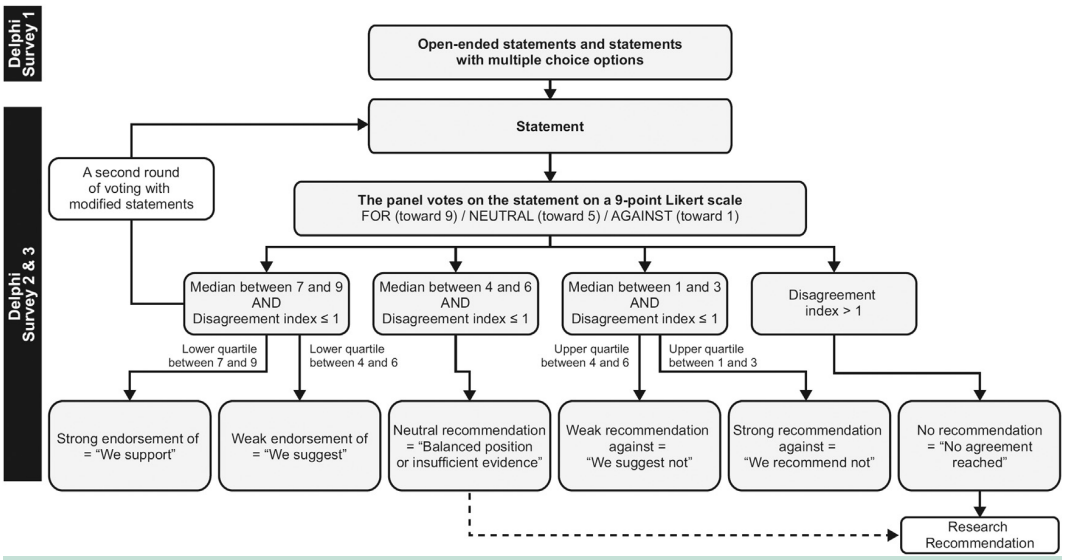

Figure 1 The modified Delphi process. Figure adapted with permission from Gosselin S, et al. *Clin Toxicol (Phila).* 2016;54(10):899-923.[12]

Table 1 Definitions

Terms	Definitions
Digoxin toxicity	• Life-threatening: toxicity can be fatal • Potentially life-threatening: toxicity may be fatal • Toxic: non–life-threatening adverse effects • At-risk: potential for adverse effects
Chronicity of digoxin exposure leading to toxicity	• Acute: bolus (intentional or inadvertent) without antecedent background use • Acute-on-chronic: bolus (intentional or inadvertent) in addition to antecedent background use with measurable levels when available • Chronic: no bolus but an increase in the digoxin level or elevated level in patient who has been taking digoxin regularly and denies taking extra doses

using the American Heart Association/American College of Cardiology (AHA/ACC) grading system.[10]

These derived statements comprised Survey 2, wherein panelists voted on a 9-point Likert scale (where 1 = "Completely Against", 5 = "Neutral", 9 = "Completely For") to quantify their level of agreement with each statement. Panelists were encouraged to provide free-text comments for each statement.

The median value, lower and upper quartile values, and disagreement index (DI) were calculated for each statement. The RAND/UCLA Appropriateness Method was used to quantify the levels of disagreement among the panelists' votes.[11] The DI, which describes the dispersion of the ratings, was calculated by dividing the interpercentile range by the interpercentile range adjusted for symmetry. For statements with agreement among the panelists (ie, DI $\leq$1), median values of 7 to 9 indicated that the panelists were in favor of/endorsed the statement, median values of 4 to 6 indicated that the panelists had a neutral position (ie, majority of panelists recommend neither for nor against the statement), and median values of 1 to 3 indicated that the panelists were against/opposed the statement (Table S4).[12] For the statements that the panelists were in favor of (ie, median values of 7 to 9), a lower quartile between 7 and 9 indicated a *strong endorsement of* the statement and a lower quartile between 4 and 6 indicated a *weak endorsement of* the statement. For the statements that the panelists were against (ie, median values of 1 to 3), an upper quartile between 1 and 3 indicated a *strong recommendation against/opposition to* the statement and an upper quartile between 4 and 6 indicated a *weak recommendation against/opposition to* the statement. Statements with no agreement reached (ie, DI >1) indicated lack of consensus (no recommendation).

Survey 2 summary statistics, DIs, recommendations, and comments were reviewed by the SC. Based on this review, 9 statements required additional feedback or revision and were included in Survey 3. The voting procedure for the panelists was the same as for Survey 2, again using the RAND/UCLA Appropriateness Method to quantify levels of disagreement.

After reviewing the results from Survey 3, the SC developed final statements including level of evidence and strength of recommendation for each statement.

RESULTS

Systematic Literature Review

Of 34,587 papers identified, 4901 duplicates were removed, 29,686 abstracts were screened, and 1368 full-text articles were reviewed for eligibility. A total of 114 publications meeting criteria were identified and included for data extraction (Figure 2**,** Table S5): 50% were prospective studies, 39% were retrospective studies, and 11% were categorized as other. These articles covered 1957 to 2021 (Figure S1), with the greatest number of publications in 1986 (n = 8), 2016 (n = 6), and 1975, 1991, and 2011 (n = 5 each). Median size of the patient population in prospective studies was 91, with total sample sizes ranging from 1 to 1835 patients. Most studies were performed outside the US (n = 74).

Survey Results

Results of Survey 1 are shown in Table S6. These responses were used to define the topics to be used as data extraction parameters for the SLR. After review of the SLR results, the SC developed 33 draft statements for Survey 2, with level of evidence noted for each statement (Tables 2 and S7). Statements were categorized by patient characteristics, concurrent medical conditions, medications that may influence digoxin toxicity, digoxin exposure, signs and symptoms of toxicity, laboratory measurements and tests, and treatment of toxicity. Based on results from Survey 2, including panelists' comments, the SC revised 9 of the 33 statements for clarity. These 9 statements comprised Survey 3 and are marked with daggers in Table 2.

Final statements with level of evidence, strength of recommendation, summary statistics, and DI are listed in Table 2. Of the 29 single-option statements, 25 had a strong endorsement, 1 had a weak endorsement (use of intravenous calcium in the management of toxicity), and 2 had a neutral recommendation (selection of digoxin immune Fab dosing

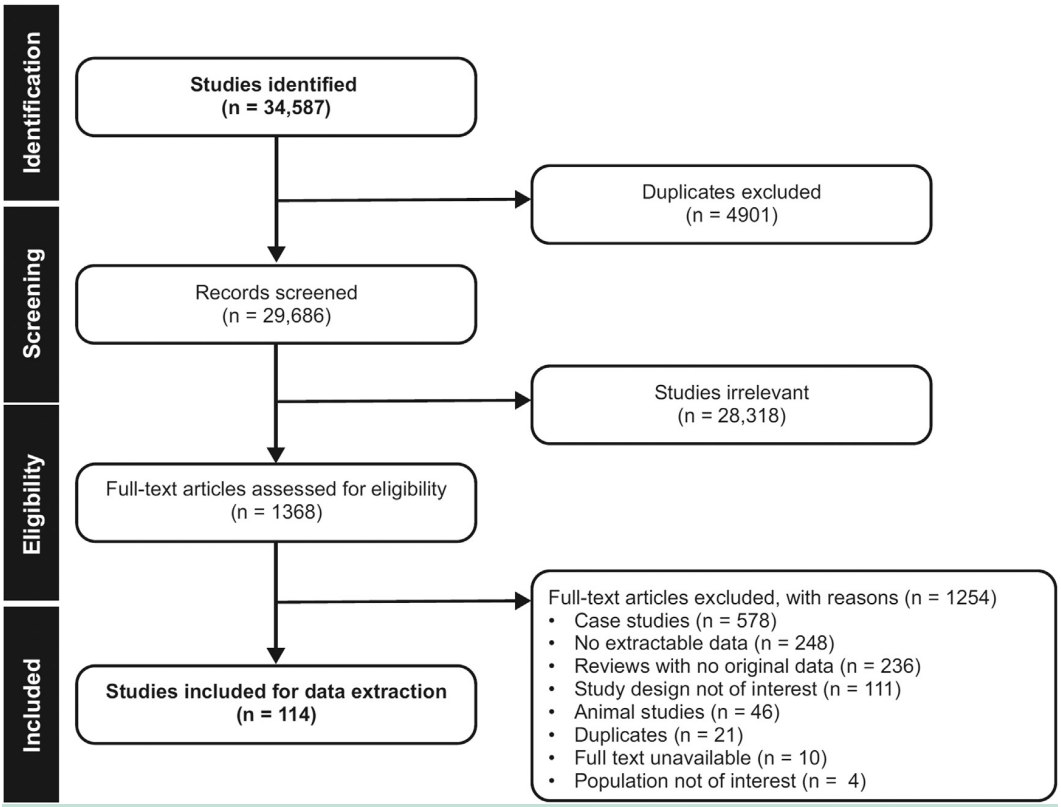

Figure 2 PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

should follow FDA-approved language; association of high magnesium levels with acute toxicity). No statements generated opposition, while 1 had no recommendation (echocardiographic evaluation in the assessment of digoxin toxicity) based on lack of consensus (ie, DI >1).

Four statements had multiple-option responses related to different levels of laboratory values. Higher serum digoxin levels and potassium values had stronger recommendations than lower values. When asked to recommend a serum digoxin concentration that would serve as an indication for digoxin immune Fab therapy in the absence of symptoms for acute or chronic digoxin ingestion, a value of >4.0 ng/mL received a weak endorsement (median 6.5-7.0, DI 0.75), whereas for a value of 4.0 ng/mL, no recommendation (ie, lack of consensus) was reached (DI 1.04), and for a value of 3.0 ng/mL, there was a weak recommendation against (median 3.0, DI 0.65). Similarly, when asked to recommend a serum potassium concentration that would serve as an indication for digoxin immune Fab therapy in adults with acute or chronic digoxin ingestion with no other reason for hyperkalemia, there was a lack of consensus (ie, no recommendation) for serum potassium concentration of 5.0-5.5 mEq/L, whereas a concentration of ≥6 mEq/L received a strong endorsement (median 8, DI 0.29).

Practical recommendations based on the final statements in Table 2 are summarized in Table 3.

DISCUSSION

Prevention, diagnosis, and management of acute and chronic digoxin toxicity remain a clinical challenge for emergency medicine physicians, cardiologists, internists, nurses, and primary care providers despite well-documented declines in the use of this agent. Reasons for the persistence of cases of toxicity are not entirely clear. Contributing factors may include its use in at-risk patient populations with multiple comorbidities (eg, elderly, heart failure, polypharmacy, renal insufficiency, myocardial conduction diseases), its narrow therapeutic window, and accepted "normal" serum levels potentially too high for some patients. For example, while the beneficial effects of digoxin appear to be related to sympatholytic effects at serum levels 0.5-0.9 ng/mL, some sources continue to list levels up to 2.0 ng/mL as "normal" or "therapeutic", including laboratory assays.[13,14]

Controversies exist about fundamental issues related to digoxin toxicity, including its definition and identification, approaches to diagnosis and management, use of adjunctive laboratory data to support or oppose diagnosis, and the threshold for antidotal treatment with digoxin immune Fab. Our results demonstrate that, although symptoms of toxicity may be nonspecific, clinical context remains an important decision-making variable in therapeutic threshold determination for use of digoxin immune Fab. There continues to

Table 2. Summary of Evidence-Based Statements for the Clinical Diagnosis and Management of Digoxin Toxicity*

Statement Number	Statement	ACC/AHA Grade	Strength of Recommendation/ Endorsement (Summary statistics)
Patient characteristics			
1†	Older age (>70 years) places patients at increased risk of digoxin toxicity even at serum digoxin levels in the "therapeutic range".	B-NR	Strong endorsement (M: 8; LQ: 8; DI: 0.13)
Concurrent medical conditions			
2†	Impaired renal function is associated with increased serum digoxin levels.	B-NR	Strong endorsement (M: 9; LQ: 8; DI: 0.13)
Digoxin exposure			
3	The nature of the digoxin exposure (acute, acute-on-chronic, chronic), including the most recent time of ingestion, must be evaluated to accurately interpret the serum digoxin levels.	B-NR	Strong endorsement (M: 9; LQ: 9; DI: 0.00)
Concurrent medications			
4	Clinicians need to consider drug-drug interactions because other medications can increase digoxin levels and/or cause increased sensitivity to the effects of digoxin, even at normal serum digoxin levels.	B-NR	Strong endorsement (M: 9; LQ: 8; DI: 0.13)
Signs and symptoms			
5	Symptoms of digoxin toxicity can be nonspecific.	C-LD	Strong endorsement (M: 8.5; LQ: 7.5; DI: 0.13)
6	Heart rate and blood pressure should be considered in the assessment of toxic or life-threatening digoxin exposure.	C-LD	Strong endorsement (M: 8; LQ: 7.5; DI: 0.13)
7	Gastrointestinal fluid loss can exacerbate dehydration, impair glomerular filtration rate (GFR), and alter the intravascular compartment size, which can affect serum digoxin levels.	C-LD	Strong endorsement (M: 8.5; LQ: 7; DI: 0.29)
Serum digoxin concentration			
8†	Serum digoxin concentrations must be measured when evaluating for digoxin toxicity.	B-NR	Strong endorsement (M: 8.5; LQ: 8; DI: 0.13)
9†	There is no consistent relationship between serum digoxin concentration and clinical effects.	B-NR	Strong endorsement (M: 8; LQ: 8; DI: 0.00)
10†	For patients with serum digoxin levels below 3 ng/mL, the diagnosis of digoxin toxicity needs to be taken in clinical context (eg, older age, underlying conduction system disease, impaired renal function).	B-NR	Strong endorsement (M: 9; LQ: 8.5; DI: 0.00)
11‡	In the absence of other clinical findings, a serum digoxin concentration of X ng/mL is an indication for digoxin Fab therapy in acute ingestions.	C-LD	3 ng/mL Weak recommendation against (M: 3; UQ: 5.5; DI: 0.65) 4 ng/mL: No recommendation (DI: 1.04) >4.0 ng/mL Weak endorsement (M: 7; LQ: 3.5; DI: 0.75)
12‡	In the absence of other clinical findings, a digoxin concentration of X ng/mL is an indication for digoxin Fab therapy in chronic ingestions.	B-NR	3 ng/mL Weak recommendation against (M: 3; UQ: 6; DI: 0.65) 4 ng/mL: No recommendation (DI: 1.04) >4.0 ng/mL Weak endorsement (M: 6.5; LQ: 4.5; DI: 0.75)

Table 2. (*Continued*)

Statement Number	Statement	ACC/AHA Grade	Strength of Recommendation/ Endorsement (Summary statistics)
Serum magnesium concentration			
13	Low magnesium levels are associated with increased sensitivity of the heart to the effects of digoxin.	B-NR	Strong endorsement (M: 8.5; LQ: 7; DI: 0.29)
14[†]	High magnesium levels in adults are associated with acute digoxin toxicity.	C-LD	Neutral recommendation (M: 5; DI: 0.52)
15[†]	Magnesium administration is associated with decreased effects of digoxin on the heart in patients with hypomagnesemia and is a temporizing measure if digoxin Fab is not immediately available.	C-LD	Strong endorsement (M: 8; LQ: 7.5; DI: 0.00)
Serum potassium concentration			
16	Hypokalemia is associated with increased effects of digoxin on the heart.	C-LD	Strong endorsement (M: 8; LQ: 7; DI: 0.29)
17[†]	High serum potassium can result from acute digoxin toxicity.	B-NR	Strong endorsement (M: 9; LQ: 9; DI: 0.00)
18[‡]	In adult patients with acute digoxin ingestion with no other reason for hyperkalemia, serum potassium concentration of X mEq/L would be indication for digoxin Fab therapy.	C-LD	5 mEq/L: No recommendation (DI: 1.56) 5.5 mEq/L: No recommendation (DI: 1.61) ≥6 mEq/L: Strong endorsement (M: 8; LQ: 6.5; DI: 0.29)
19[‡]	In adult patients on chronic digoxin therapy that have signs or symptoms of digoxin toxicity with no other reason for hyperkalemia, serum potassium concentration of X mEq/L would be indication for digoxin Fab therapy.	C-LD	5 mEq/L: No recommendation (DI: 1.56) 5.5 mEq/L: No recommendation (DI: 1.61) ≥6 mEq/L: Strong endorsement (M: 8; LQ:6; DI: 0.29)
Echocardiographic and electrocardiographic findings			
20	Echocardiogram evaluation should be part of the assessment of digoxin toxicity.		No recommendation (DI: 1.56)
21	Electrocardiographic findings can be nonspecific in a patient with digoxin toxicity.	B-NR	Strong endorsement (M: 9; LQ: 7; DI: 0.29)
22	Heart rhythm abnormalities, including bradycardia/atrioventricular block and some tachyarrhythmias (eg, paroxysmal atrial tachycardia [PAT] with block) are associated with digoxin toxicity.	B-NR	Strong endorsement (M: 9; LQ: 8; DI: 0.13)
Treatment for digoxin toxicity, short- and long-term outcomes			
23[†]	Activated charcoal is effective in shortening the elimination half-life of digoxin in cases of acute ingestion.	C-LD	Strong endorsement (M: 8; LQ: 7; DI: 0.16)
24	Management of and triggers for digoxin Fab use differ based on the chronicity of toxicity (acute or chronic).	C-LD	Strong endorsement (M: 8.5; LQ: 7.5; DI: 0.13)
25	Selection of digoxin Fab dosing should follow FDA-approved language as outlined in the digoxin Fab product guide.	B-NR	Neutral recommendation (M: 5.5; DI: 0.97)
26	Digoxin Fab is first-line treatment for life-threatening digoxin exposure.	B-NR	Strong endorsement (M: 9; LQ: 7.5; DI: 0.13)
27	Digoxin-associated bradyarrhythmia should be treated antidotally rather than with a temporary transvenous pacemaker.	C-LD	Strong endorsement (M: 7.5; LQ: 6.5; DI: 0.29)
28	Digoxin Fab antidotal treatment decreases incidence of death with life-threatening digoxin toxicity.	B-NR	Strong endorsement (M: 8; LQ: 8; DI: 0.13)
29	Digoxin Fab antidotal therapy for digoxin toxicity may decrease total medical costs.	B-NR	Strong endorsement (M: 7.5; LQ: 6.5; DI: 0.16)

Table 2. (*Continued*)

Statement Number	Statement	ACC/AHA Grade	Strength of Recommendation/ Endorsement (Summary statistics)
30	Digoxin maintenance therapy should not be restarted in the acute setting following a presentation with digoxin toxicity that required digoxin Fab antidotal treatment, except in rare circumstances and after risk-benefit assessment.	C-LD	Strong endorsement (M: 8; LQ: 7; DI: 0.29)
31	Reoccurrence of acute heart failure symptoms is unlikely to occur after antidotal therapy with digoxin Fab.	B-NR	Strong endorsement (M: 8; LQ: 6.5; DI: 0.16)
Role of calcium in the management of patients with digoxin toxicity			
32	Intravenous calcium is not helpful in the treatment of digoxin-induced hyperkalemia.	C-LD	Strong endorsement (M: 8; LQ: 6; DI: 0.29)
33	Intravenous calcium may be harmful in the treatment of the cardiac effects of digoxin.	C-LD	Weak endorsement (M: 7; LQ: 4.5; DI: 0.75)

The quality of the available evidence supporting each statement was determined using the ACC/AHA Task Force in Clinical Practice Guidelines methodology (B-NR: Level B nonrandomized; C-LD: Level C limited data). The strength of recommendation is based on consensus obtained from the modified Delphi process. Summary statistics for the voting results include median (M), lower quartile (LQ), upper quartile (UQ), and disagreement index (DI). The RAND/UCLA Appropriateness method was used to quantify the levels of disagreement among the voting results.

*To view the reference support for each statement, please see Supplemental Table S7.

†Statements revised based on feedback from panelists during Survey 2 and included in Survey 3. Only revised statements from Survey 3, summary statistics, and recommendations based on this survey are included in this table.

‡Multi-option survey questions: recommendation and voting results summary statistics for each option have been included.

be uncertainty about thresholds for indication of digoxin immune Fab therapy based on serum digoxin concentration in both acute and chronic settings, with a weak endorsement for a threshold concentration of >4 ng/mL. With regards to serum potassium levels, panelists support concentrations ≥6 mEq/L as an indication for digoxin immune Fab therapy when other causes for hyperkalemia are ruled out. The panelists' recommendation on the role of magnesium in acute digoxin toxicity was neutral, and there was weak endorsement for the statement that intravenous calcium may be harmful in the treatment of cardiac effects of digoxin. It is unlikely that double-blinded studies will be performed to further elucidate when and how calcium should be incorporated into treatment algorithms, though observational cohort or randomized open-label studies should be considered. Until affirmative data are generated, it may be reasonable to avoid its use, especially because infusion of calcium may be harmful in this setting.

The many areas of agreement included the need to consider time of ingestion and nature of the exposure (ie, acute, acute-on-chronic, chronic) in order to accurately interpret digoxin levels. Whether clinicians fully understand the importance of these factors is not clear, and ongoing educational efforts should target the recognition and correct assessment of digoxin toxicity.

Two recent papers have weighed evidence to suggest guideline statements related to digoxin toxicity.[15,16] An AHA update on management of patients with cardiac arrest or life-threatening toxicity due to poisoning focused on North American healthcare professionals treating critically ill adults and children[15] and provided levels of evidence and class of recommendations; authors strongly recommended administration of digoxin immune Fab as it can reverse life-threatening arrhythmias from digoxin poisoning. Andrews et al[16] used a modified Delphi technique to reach consensus among participants based in Western Europe. While this paper did not list level of evidence or strength of recommendations and did not provide detail on the literature review process, the authors recommended immediate treatment with digoxin immune Fab for life-threatening digoxin toxicity and treatment with digoxin immune Fab in patients with non–life-threatening digoxin toxicity only after evaluation of serum digoxin levels.[16]

Similar to our strong endorsement, both the AHA update[15] and Andrews et al[16] labeled digoxin immune Fab as first-line treatment for life-threatening digoxin toxicity. These papers suggested dosing guidelines that differ from the FDA-approved language.[15,16] Similarly, our panel had a neutral recommendation for FDA-approved dosing regimens, suggesting a need for further research in this area. We posit that some uncertainty may arise from perceived cost considerations related to the use of digoxin immune Fab for non−life-threatening toxicity, which currently is not an FDA-approved indication. Whether smaller doses (ie, fewer vials) can be safely used to mitigate toxicity that is not life-threatening while limiting cost is unclear. An earlier study estimated cost per life-year saved between $1900 and $5400 (based on 1991 US dollars).[17] There has been speculation that the incremental cost-effectiveness ratio decreases with use of digoxin immune Fab to treat patients with less-serious toxicity,[17] but definitive data are lacking.

While recommendations by Andrews et al[16] align with the present work in other areas, including lack of a consistent relationship between serum digoxin concentration and clinical effects, there are areas of divergence. Regarding levels of hyperkalemia as an indication for digoxin immune Fab therapy, Andrews et al noted a potassium level of >6.5 mmol/L,[16] which is greater than the levels queried in

Table 3 Practical Recommendations

- When assessing a patient for digoxin toxicity, our findings support consideration of the patient's age, renal function, nature of exposure (acute, acute-on-chronic, chronic), serum digoxin level, most-recent time of digoxin ingestion, potential drug-drug interactions with digoxin, heart rate, blood pressure, gastrointestinal fluid loss or dehydration, serum magnesium level, and serum potassium level.
- With regard to treatment with digoxin immune Fab, our findings support its use 1) in the setting of life-threatening digoxin exposure to decrease the likelihood of death; 2) in the absence of other clinical findings, treatment when the serum digoxin concentration is >4 ng/mL in patients with acute or chronic digoxin ingestion; 3) in adult patients with acute or chronic digoxin ingestion and suspected digoxin toxicity with no other reason for hyperkalemia, when the serum potassium concentration is ≥6 mEq/L; and 4) in patients with digoxin-associated bradyarrhythmia rather than a temporary transvenous pacemaker.
- Our findings support use of activated charcoal in acute ingestion to shorten the elimination half-life of digoxin.
- Our findings recommend that digoxin maintenance therapy not be restarted in the acute setting following a presentation with digoxin toxicity that required digoxin immune Fab treatment, except in rare circumstances and after risk-benefit assessment.

Source: Tables 2; S7

our survey. Our results include strong endorsement of the use of digoxin immune Fab rather than temporary pacemaker placement in the setting of digoxin-associated bradyarrhythmia (median 7.5, lower quartile 6.5, DI 0.29); the AHA and Andrews et al studies[15,16] noted weak support for atropine and pacing, but both affirm digoxin immune Fab as first-line treatment. The AHA and Andrews et al studies[15,16] also mention use of medications to treat ventricular arrhythmias due to toxicity; our study did not include similar statements, based on the paucity of evidence in our SLR. Further, both AHA and Andrews et al[15,16] noted that extracorporeal treatments to enhance the elimination of digoxin are not recommended. Our study did not address this option, as hemodialysis is not effective given significant distribution of digoxin in tissues (as opposed to blood) in patients who have reached steady state, and dialysis will not facilitate removal of the digoxin-digoxin immune Fab complex.

Limitations

The literature on digoxin toxicity remains limited in quality and scope, with few appropriately powered studies to inform practice and no randomized controlled trials. With a limited number of prospective studies and low likelihood of generation of new data, clinicians must rely on consensus statements developed with expert opinion. A strength of the current exercise was performance of a focused SLR, which informed development of the statements. Nevertheless, data were lacking in several areas, likely contributing to clinical uncertainty and/or disagreement among panelists. While we engaged experts in cardiology, nursing, toxicology and emergency medicine, other clinicians who may be the first to diagnose digoxin toxicity, such as internists and primary care providers, were not included. Not all panelists who responded to Survey 2 participated in Survey 3 and neither included case vignettes. Further, the potential role of shared decision-making in the management of patients with suspected or confirmed digoxin toxicity was not specifically addressed.

CONCLUSIONS

Results of this SLR of more than 30,000 studies and subsequent modified Delphi process provide additional clarity and indicate a strong recommendation for use of digoxin immune Fab as a first-line treatment for life-threatening exposure, aligning with recent guideline statements. However, our findings revealed lack of support for administering digoxin immune Fab for digoxin concentrations less than 4 ng/mL and potassium concentrations of 5.0-5.5 mEq/L in the absence of clinical evidence for toxicity. There was weak endorsement for the statement that intravenous calcium may be harmful in the treatment of the cardiac effects of digoxin, highlighting the need for additional investigation. It is unlikely that randomized double-blind placebo-controlled trials that can guide evidence-based practices will be designed, as they would likely be neither ethical nor practical. Rather, clinicians will continue to rely on observational cohorts or small randomized open label studies, or interpretation of literature from the distant past to inform practice. Further research is also needed to evaluate the pharmaco-economics of the use of digoxin immune Fab for cases of toxicity that require in-hospital monitoring including telemetry. Nevertheless, significant areas of consensus are described and, through dissemination to clinicians, may contribute to improvements in both diagnostic and therapeutic strategies aimed at reducing morbidity and mortality associated with digoxin toxicity.

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REFERENCES

1. Alahmed AA, Lauffenburger JC, Vaduganathan M, et al. Contemporary trends in the use of and expenditures on digoxin in the United States. *Am J Cardiovasc Drugs* 2022;22(5):567–75.
2. See C, Wheelock KM, Caraballo C, et al. Patterns of digoxin prescribing for Medicare beneficiaries in the United States 2013-2019. *Am J Med Open* 2023;10:100048.
3. See I, Shehab N, Kegler SR, et al. Emergency department visits and hospitalizations for digoxin toxicity: United States, 2005 to 2010. *Circ Heart Fail* 2014;7(1):28–34.
4. Hauptman PJ, Blume SW, Lewis EF, Ward S. Digoxin toxicity and use of digoxin inmmune fab: insights from a national hospital database. *JACC: Heart Failure* 2016;4(5):357–64.
5. Angraal S, Nuti SV, Masoudi FA, et al. Digoxin use and associated adverse events among older adults. *Am J Med* 2019;132(10):1191–8.

6. Peters AE, Chiswell K, Hofmann P, et al. Characteristics and outcomes of suspected digoxin toxicity and immune fab treatment over the past two decades-2000-2020. *Am J Cardiol* 2022;183:129–36.
7. Chan BS, Isbister GK, Page CB, et al. Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4). *Clin Toxicol (Phila)* 2019;57(7):638–43.
8. Kirrane BM, Olmedo RE, Nelson LS, et al. Inconsistent approach to the treatment of chronic digoxin toxicity in the United States. *Human Exp Toxicol* 2009;28:285–92.
9. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160.
10. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;67(13):1572–4.
11. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND; 2001.
12. Gosselin S, Hoegberg LC, Hoffman RS, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. *Clin Toxicol (Phila)* 2016;54(10):899–923.
13. Hauptman PJ, McCann P, Ramirez Romero JM, Mayo M. Reference laboratory values or digoxin following publication of Digitalis Investigation Group (DIG) trial data. *JAMA Intern Med* 2013;173(16):1552–4.
14. David MNV, Shetty M. Digoxin. January 19, 2023. https://www.ncbi.nlm.nih.gov/books/NBK556025/?report=printable. Accessed May 24, 2024.
15. Lavonas EJ, Akpunonu PD, Arens AM, et al. 2023 American Heart Association focused update on the management of patients with cardiac arrest or life-threatening toxicity due to poisoning: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2023;148(16):e149–84.
16. Andrews P, Anseeuw K, Kotecha D, et al. Diagnosis and practical management of digoxin toxicity: a narrative review and consensus. *Eur J Emerg Med* 2023;30(6):395–401.
17. Mauskopf JA, Wenger TL. Cost-effectiveness analysis of the use of digoxin immune Fab (ovine) for treatment of digoxin toxicity. *Am J Cardiol* 1991;68(17):1709–14.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2024.08.018

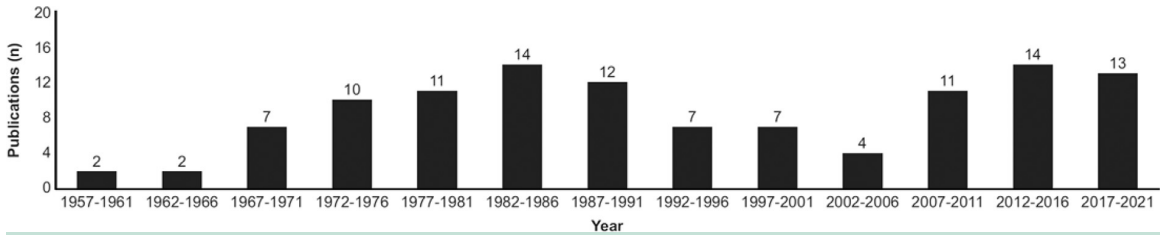

Figure S1. Studies included by year (n = 114)

Table S1 Steering Committee and Panelist Membership

	Project launch	Survey 1	Survey 2	Survey 3
Steering Committee	Hack, Hauptman, Hoffman, Gosselin	Hack, Hauptman, Hoffman	Hack, Hauptman	Hack, Hauptman, Wingate
Other Panelists		Adams, Cocchio, Gosselin, Kirrane, Levy, Ng, Nordt, Rella, Rich, Sample, Wingate, Zolty (n = 12)	Cocchio, Kirrane, Levy, Ng, Nordt, Rella, Rich, Sample, Wingate, Zolty (n = 10)	Cocchio, Kirrane, Levy, Ng, Nordt, Rella, Rich, Sample, Zolty (n = 9)

Table S2 Systematic Literature Review Strategy

Database	Search Terms
PubMed	(("digoxin"[MeSH Terms] OR "digitalis"[MeSH Terms] OR "digitoxin"[MeSH Terms] OR "digox*"[All Fields] OR "digitalis*"[All Fields] OR "digitaliz*"[All Fields] OR "digitox*"[All Fields]) AND (("ventric*"[All Fields] AND "fibrillation*"[All Fields]) OR "asystol*"[All Fields] OR "ectop*"[All Fields] OR ("bidirect*"[All Fields] AND "tachycardi*"[All Fields]) OR "bradycardi*"[All Fields] OR (("heart"[All Fields] OR "cardi*"[All Fields] OR "atrioventricul*"[All Fields] OR "AV"[All Fields] OR "branch"[All Fields]) AND ("arrest*"[All Fields] OR "block*"[All Fields])) OR "RBBB"[All Fields] OR "LBBB"[All Fields] OR "hyperkalemi*"[All Fields] OR "hypokalemi*"[All Fields] OR (("renal*"[All Fields] OR "kidney*"[All Fields]) AND ("diseas*"[All Fields] OR "fail*"[All Fields])) OR "visio*"[All Fields] OR "visua*"[All Fields] OR "halo*"[All Fields] OR ("color*"[All Fields] AND ("discrimin*"[All Fields] OR "perce*"[All Fields])) OR ("sinu*"[All Fields] AND "arrest*"[All Fields]) OR ("sine*"[All Fields] AND "wave*"[All Fields]) OR "toxic*"[All Fields] OR "poison*"[All Fields] OR "intoxic*"[All Fields] OR "overdos*"[All Fields] OR ("advers*"[All Fields] AND "event*"[All Fields]) OR ("advers*"[All Fields] AND "effect*"[All Fields]) OR ("side*"[All Fields] AND "effect*"[All Fields]) OR ("antibod*"[All Fields] OR "immun*"[All Fields])) AND ("English"[Language] OR "Spanish"[Language] OR "Italian"[Language] OR "German"[Language] OR "French"[Language])) NOT (("digoxin"[MeSH Terms] OR "digitalis"[MeSH Terms] OR "digitoxin"[MeSH Terms] OR "digox*"[All Fields] OR "digitalis*"[All Fields] OR "digitaliz*"[All Fields] OR "digitox*"[All Fields]) AND (("ventric*"[All Fields] AND "fibrillation*"[All Fields]) OR "asystol*"[All Fields] OR "ectop*"[All Fields] OR ("bidirect*"[All Fields] AND "tachycardi*"[All Fields]) OR "bradycardi*"[All Fields] OR (("heart"[All Fields] OR "cardi*"[All Fields] OR "atrioventricul*"[All Fields] OR "AV"[All Fields] OR "branch"[All Fields]) AND ("arrest*"[All Fields] OR "block*"[All Fields])) OR "RBBB"[All Fields] OR "LBBB"[All Fields] OR "hyperkalemi*"[All Fields] OR "hypokalemi*"[All Fields] OR (("renal*"[All Fields] OR "kidney*"[All Fields]) AND ("diseas*"[All Fields] OR "fail*"[All Fields])) OR "visio*"[All Fields] OR "visua*"[All Fields] OR "halo*"[All Fields] OR ("color*"[All Fields] AND ("discrimin*"[All Fields] OR "perce*"[All Fields])) OR ("sinu*"[All Fields] AND "arrest*"[All Fields]) OR ("sine*"[All Fields] AND "wave*"[All Fields]) OR "toxic*"[All Fields] OR "poison*"[All Fields] OR "intoxic*"[All Fields] OR "overdos*"[All Fields] OR ("antibod*"[All Fields] OR "immun*"[All Fields])) AND ("English"[Language] OR "Spanish"[Language] OR "Italian"[Language] OR "German"[Language] OR "French"[Language]))
Embase	(('digoxin'/exp OR 'digitoxin'/exp OR 'digitalis'/exp OR digox* OR digitox* OR digitalis* OR digitaliz*) AND (ectop* OR (ventric* NEXT/2 fibrillation*) OR asystol* OR (bidirect* NEXT/2 tachycardi*) OR bradycardi* OR (('heart' OR cardi* OR atrioventricul* OR 'av' OR 'branch') NEXT/1 (arrest* OR block*)) OR hyperkalemi* OR hypokalemi* OR ((renal* OR kidney*) NEXT/1 (diseas* OR fail*)) OR visio* OR visua* OR halo* OR (color* NEAR/2 (discrimin* OR perce*)) OR (sinu* NEXT/1 arrest*) OR (sin* NEXT/1 wave*) OR 'rbbb' OR 'lbbb' OR toxic* OR poison* OR intoxic* OR overdos* OR ((advers* OR side*) NEXT/1 (event* OR effect*)) OR antibod* OR (immun* NEXT/1 (fragment* OR treatment OR therapy))) AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim)

Table S2 (*Continued*)

Database	Search Terms
	AND [humans]/lim) NOT (('digoxin'/exp OR 'digitoxin'/exp OR 'digitalis'/exp OR digox* OR digitox* OR digitalis* OR digitaliz*) AND (ectop* OR (ventric* NEXT/2 fibrillation*) OR asystol* OR (bidirect* NEXT/2 tachycardi*) OR bradycardi* OR (('heart' OR cardi* OR atrioventricul* OR 'av' OR 'branch') NEXT/1 (arrest* OR block*)) OR hyperkalemi* OR hypokalemi* OR ((renal* OR kidney*) NEXT/1 (diseas* OR fail*)) OR visio* OR visua* OR halo* OR (color* NEAR/2 (discrimin* OR perce*)) OR (sinu* NEXT/1 arrest*) OR (sin* NEXT/1 wave*) OR 'rbbb' OR 'lbbb' OR toxic* OR poison* OR intoxic* OR overdos* OR antibod* OR (immun* NEXT/1 (fragment* OR treatment OR therapy))) AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim OR [spanish]/lim) AND [humans]/lim)
LILACS	Search #1 (digoxin OR digitoxin OR digitalis) AND (((toxic* OR poison* OR intoxic* OR overdos*) OR (((adverse event*) OR (adverse effect*)) OR (side effect*)))) AND human AND (db:("LILACS") AND la:("en" OR "de" OR "fr" OR "es" OR "it")) (full; N=55; n=17 to "subtracted" library)
	Search #2: (digoxin OR digitoxin OR digitalis) AND (toxic* OR poison* OR intoxic* OR overdos*) AND human AND (db:("LILACS") AND la:("en" OR "de" OR "fr" OR "es" OR "it"))
Google Scholar	Digoxin AND (toxic* OR poison* OR intoxic* OR overdos*) AND human (~18,500 results; language limits to English, Spanish, French, German, and Italian)
Congresses	Digoxin; either via journal websites or PDF versions of abstract books
Other grey literature	Digoxin AND (toxic* OR poison*)[†]

†Terms for toxicity and poisoning were adapted/written out depending on the search capabilities of the database.
LILACS = Latin American and Caribbean Center on Health Sciences Information.

Table S3 Systematic Literature Review Strategy

Time Frames and Databases

Type of Database	Time Frame	Databases
Publications	Inception to Oct 2021	• Embase • PubMed • LILACS
Congresses	2016 to Oct 2021	• ACC • ACCP • ACEP • ACMT • AHA • ASHP • EAPCCT • ESC • HFSA • NACCT • SHM
Clinical trials	2016 to Oct 2021	• ClinicalTrials.gov • WHO • EudraCT • ANZCTR
Other grey literature	1999 (or Inception if after 1999) to Oct 2021	• Google Scholar* • Open Grey • NIH RePORTER • AHRQ • OAIster

Table S3 (*Continued*)

Time Frames and Databases

Type of Database	Time Frame	Databases
Screening Considerations		
Title/abstract screening	• Included — Original research, reviews, editorials, book chapters, and commentaries included to determine if they contain original data • Excluded — Publications of nonhuman or in vitro studies — Studies of toxicity due to non-pharmacologic (eg, non-digoxin, or non-digitalis) cardiac glycosides (ie, no plant or animal cardiac glycosides, no other digitalis-like poisons) — Patients with poly overdose — Case reports prior to 1990	
Full text screening	• Inclusion criteria from Survey 1 results • Primary criteria for selection of publications for data extraction — Is there information and/or data in the article that the panelists want based on Survey 1 results? — Is the publication reporting original data? — If this publication is a case report, is it unusual and interesting?	

*1995 to presentLILACS = Latin American and Caribbean Center on Health Sciences Information.

Table S4. Assessment of Strength of Recommendation From Survey Responses

Recommendation	Disagreement Index	Median	Q1	Q3
In Favor				
Strong endorsement of	≤1	7-9	7-9	-
Weak endorsement of	≤1	7-9	4-6	-
Neutral Recommendation	≤1	4-6	-	-
Against				
Strong recommendation against	≤1	1-3	-	1-3
Weak recommendation against	≤1	1-3	-	4-6
No Recommendation	>1	-	-	-

Disagreement index is calculated by dividing the interpercentile range by the interpercentile range adjusted for symmetry.
Q1 = lower bound of the interquartile range; Q3 = upper bound of the interquartile range.

Table S5 List of Studies From SLR

References

Abad-Santos FF, Carcas AJ, Ibáñez C, Frías J. Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity. *Ther Drug Monit*. 2000;22(2):163-168.

Al Lawati I, Cormier M, Gosselin S. Variability of international clinical toxicologists recommendations concerning the use of digoxin-specific antibody fragments [abstract]. *Clin Toxicol*. 2017;55(7):708-709.

Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation*. 1990;81(6):1744-1752.

Arbabian H, Lee HM, Graudins A. Elderly patients with suspected chronic digoxin toxicity: a comparison of clinical characteristics of patients receiving and not receiving digoxin-Fab. *Emerg Med Australas*. 2018;30(2):242-248.

Aronson JK, Ford AR. The use of colour vision measurement in the diagnosis of digoxin toxicity. *Q J Med*. 1980;49(195):273-282.

Beller GA, Hood WB Jr, Smith TW, Abelmann WH, Wacker WE. Correlation of serum magnesium levels and cardiac digitalis intoxication. *Am J Cardiol*. 1974;33(2):225-229.

Beller GA, Smith TW, Abelmann WH, Haber E, Hood WB Jr. Digitalis intoxication. A prospective clinical study with serum level correlations. *N Engl J Med*. 1971;284(18):989-997.

Bilbault P, Oubaassine R, Rahmani H, et al. Emergency step-by-step specific immunotherapy in severe digoxin poisoning: an observational cohort study. *Eur J Emerg Med*. 2009;16(3):145-149.

Table S5 (*Continued*)

References

Bismuth C, Gaultier M, Conso F, Efthymiou ML. Hyperkalemia in acute digitalis poisoning: prognostic significance and therapeutic implications. *Clin Toxicol*. 1973;6(2):153-162.

Bismuth C, Motte G, Conso F, Chauvin M, Gaultier M. Acute digitoxin intoxication treated by intracardiac pacemaker: experience in sixty-eight patients. *Clin Toxicol*. 1977;10(4):443-456.

Bohmer T, Røseth A. Prolonged digitoxin half-life in very elderly patients. *Age Ageing*. 1998;27(2):222-224.

Boman K. Digitalis intoxication in geriatric in-patients. A prospective clinical study of the value of serum digitalis concentration measurement. *Acta Med Scand*. 1983;214(5):345-351.

Calypso G, Emmanuel B, Lucie C, Nicolas D, Sebastian V, Bruno M. Chronic digitalis poisoning treated with anti-digoxin Fab: a critical analysis of treatment indications and patient outcome [abstract P-144]. *Ann Intensive Care*. 2018;8(suppl 1):144.

Caparrós SA, Salgado García E, Calpe Perarnau X, et al. Immediate and 30 days mortality in digoxin poisoning cases attended in the Hospital Emergency Services of Catalonia, Spain. *Emergencias*. 2019;31(1):39-42.

Carosella L, Pahor M, Pedone C, Manto A, Carbonin PU, Gruppo Italiano di Farmacovigilanza nell'Anziano. Digitalis in the treatment of heart failure in the elderly. The GIFA study results. *Arch Gerontol Geriatr*. 1996;23(3):299-311.

Chan AL, Wang MT, Su CY, Tsai FH. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: a population-based study. *Eur J Clin Pharmacol*. 2009;65(12):1237-1243.

Chan BSH, Chiew AL, Page CB, O'Leary M, Isbister GK, Buckley NA. Acute digoxin overdose and response to antibody (DORA study) [abstract 18]. *Clin Toxicol*. 2017:378.

Chan BS, Isbister GK, Chiew A, Isoardi K, Buckley NA. Clinical experience with titrating doses of digoxin antibodies in acute digoxin poisoning. (ATOM-6). *Clin Toxicol (Phila)*. 2022;60(4):433-439.

Chan BS, Isbister GK, O'Leary M, Chiew A, Buckley NA. Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1). *Clin Toxicol (Phila)*. 2016;54(6):488-494.

Chan BS, Isbister GK, Page CB, Isoardi KZ, Chiew AL, Kirby KA, Buckley NA. Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4). *Clin Toxicol (Phila)*. 2019;57(7):638-643.

Chan BS, O'Leary M, Isbister G, Buckley NA. The use of digoxin-specific antibodies in chronic digoxin poisoning [abstract 15]. *Clin Toxicol*. 2015;53(4):241.

Charfi R, Ben Sassi M, Gaies E, Jebabli N, Daghfous R, Trabelsi S. Digoxin therapeutic drug monitoring: age influence and adverse events. *Tunis Med*. 2020;98(1):35-40.

Chen JY, Liu PY, Chen JH, Lin LJ. Safety of transvenous temporary cardiac pacing in patients with accidental digoxin overdose and symptomatic bradycardia. *Cardiology*. 2004;102(3):152-155.

Chhabra N, Valento M, Bryant SM, Aks SE. Digoxin-specific antibody fragment dosing: a case series. *Am J Ther*. 2015;23(6):e1597-e1601.

Cobo Sacristan S, Leiva Badosa E, Miquel Zurita ME, et al. Analysis of patients with digoxin intoxication admitted to hospital as emergencies [abstract PKP-007]. *Eur J Hosp Pharm*. 2014;21(Supplement 1):A139.

Dally S, Bismuth C, Alperovitch A, Lagier G, Scherrmann JM, Elkhouly M. Prognostic factors in acute digitalis poisoning. Article in French. *Schweiz Med Wochenschr*. 1982;112(31-32):1113-1116.

Detweiler DK, Trautvetter EECG scoring system for detection of digitoxin or digitalis poisoning. Article in German. *Berl Munch Tierarztl Wochenschr*. 1980;93(21):424-426.

DiDomenico RJ, Walton SM, Sanoski CA, Bauman JL. Analysis of the use of digoxin immune fab for the treatment of non-life-threatening digoxin toxicity. *J Cardiovasc Pharmacol Ther*. 2000;5(2):77-85.

Doering W, König E, Sturm W. Digitalis intoxication: specificity and significance of cardiac and extracardiac symptoms. Part II. Patients with extracardiac symptoms of digitalis intoxications. Article in German. *Z Kardiol*. 1977;66(3):129-137.

Dubnow MH, Burchell HB. A comparison of digitalis intoxication in two separate periods. *Ann Intern Med*. 1965;62:956-965.

El-Sarnagawy GN, El Sharkawy SI, Helal NE. Predictive factors for recurrence of serious arrhythmias in patients with acute digoxin poisoning. *Cardiovasc Toxicol*. 2021;21(10):835-847.

Eraker SA, Sasse L. The serum digoxin test and digoxin toxicity: a Bayesian approach to decision making. *Circulation*. 1981;64(2):409-420.

Evered DC, Chapman C. Plasma digoxin concentrations and digoxin toxicity in hospital patients. *Br Heart J*. 1971;33(4):540-545.

Farrell N, Hack J. Lady stone heart? [abstract #87] *J Med Toxicol*. 2017;13(1):33.

Gaultier M, Fournier E, Efthymiou ML, Frejaville JP, Jouannot P, Dentan M. Acute digitalis poisoning (70 cases).Article in French. *Bull Mem Soc Med Hop Paris*. 1968;119(3):247-274.

Gaultier M, Welti JJ, Bismuth C, Motte G, Conso F, Chauvin M. Severe digitalis intoxication. Prognostic factors. Value and limitations of electrosystolic pacemaking (apropos of 133 cases). Article in French. *Ann Med Interne (Paris)*. 1976;127(10):761-766.

Gheshlaghi F, Wong A, Dorooshi G, et al. Ten years of experience in treating patients with digoxin toxicity without using digoxin fab antibody. *Int J Med Toxicol Forensic Med*. 2021;11(1):31239.

Gomes T, Mamdani MM, Juurlink DN. Macrolide-induced digoxin toxicity: a population-based study. *Clin Pharmacol Ther*. 2009;86(4):383-386.

Gotsman MS, Schrire V. Toxicity—a frequent complication of digitalis therapy. *S Afr Med J*. 1966;40(25):590-592.

Table S5 (*Continued*)

References

Hauptman PJ, Blume SW, Lewis EF, Ward S. Digoxin toxicity and use of digoxin immune fab: insights from a national hospital database. *JACC: Heart Fail*. 2016;4(5):357-364.

Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin Immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol*. 1991;17(3):590-598.

Howard D, Smith CI, Stewart G, et al. A prospective survey of the incidence of cardiac intoxication with digitalis in patients being admitted to hospital and correlation with serum digoxin levels. *Aust N Z J Med*. 1973;3(3):279-284.

Ibañez C, Carcas AJ, Frias J, Abad F. Activated charcoal increases digoxin elimination in patients. *Int J Cardiol*. 1995;48(1):27-30.

Jitapunkul S, Kongsawat V, Sutheparak S. Digoxin toxicity in Thai medical patients: clinical manifestations and an appropriate diagnostic serum level. *Southeast Asian J Trop Med Public Health*. 2002;33(3):608-612.

Joos HA, Johnson JL. Digitalis intoxication in infancy and childhood. *Pediatrics*. 1957;20(5, Part 1):866-876.

Jorgensen AW, Sorensen OH. Digitalis intoxication. A comparative study on the incidence of digitalis intoxication during the periods 1950-52 and 1964-66. *Acta Med Scand*. 1970;188(3):179-183.

Kirilmaz B, Saygi S, Gungor H, et al. Digoxin intoxication: an old enemy in modern era. *J Geriatr Cardiol*. 2012;9(3):237-242.

Kirkpatrick CH. Allergic histories and reactions of patients treated with digoxin immune Fab (ovine) antibody. The Digibind Study Advisory Panel. *Am J Emerg Med*. 1991;9(2 Suppl 1):7-10.

Kockova R, Skvaril J, Cernohous M, Maly M, Kocka V, Linhart A. Five year two center retrospective analysis of patients with toxic digoxin serum concentration. *Int J Cardiol*. 2011;146(3):447-448.

Koren G, Parker R. Interpretation of excessive serum concentrations of digoxin in children. *Am J Cardiol*. 1985;55(9):1210-1214.

LaFountain N, Marino R, Abesamis M. Evaluating the need for digoxin immune Fab (ovine) therapy in chronic digoxin toxicity [abstract 064]. *J Med Toxicol*. 2019;15:72.

Lapostolle F, Borron SW, Verdier C, et al. Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med*. 2008;36(11):3014-3018.

Lapostolle F, Borron SW, Verdier C, et al. Assessment of digoxin antibody use in patients with elevated serum digoxin following chronic or acute exposure. *Intensive Care Med*. 2008;34(8):1448-1453.

Lapostolle F, Devallière E, Alhéritière A, Adnet F. Relation between creatinine level and kalaemia in patients with digitalis poisoning. Article in French. *Presse Med*. 2012;41(12 pt 1):1297-1299.

Lecointre K, Pisanté L, Fauvelle F, Mazouz S. Digoxin toxicity evaluation in clinical practice with pharmacokinetic correlations. *Clin Drug Invest*. 2001;21(3):225-232.

Lely AH, van Enter CH. Large-scale digitoxin intoxication. *Br Med J*. 1970;3(5725):737-740.

Levine M, Nikkanen H, Pallin DJ. The effects of intravenous calcium in patients with digoxin toxicity. *J Emerg Med*. 2011;40(1):41-46.

Lewander WJ, Gaudreault P, Einhorn A, Henretig FM, Lacouture PG, Lovejoy FHJ. Acute pediatric digoxin ingestion: a ten-year experience. *Am J Dis Child*. 1986;140(8):770-773.

Limon G, Ersoy G, Oray NC, Bayram B, Limon O. Retrospective evaluation of patients with elevated digoxin levels at an emergency department. *Turk J Emerg Med*. 2016;16(1):17-21.

Listiawan M, Lackey G, Alsop J, Albertson T, Inciardi J, Ofstad W. A 10 year retrospective review of digoxin immune Fab use in digoxin exposures [abstract 9]. *Clinical Toxicology*. 2012;50(7):578.

Manini AF, Nelson LS, Hoffman RS. Prognostic utility of serum potassium in chronic digoxin toxicity: a case-control study. *Am J Cardiovasc Drugs*. 2011;11(3):173-178.

Marik PE, Fromm L. A case series of hospitalized patients with elevated digoxin levels. *Am J Med*. 1998;105(2):110-115.

Mauskopf JA, Wenger TL. Cost-effectiveness analysis of the use of digoxin immune Fab (ovine) for treatment of digoxin toxicity. *Am J Cardiol*. 1991;68(17):1709-1714.

Miura T, Kojima R, Sugiura Y, Mizutani M, Takatsu F, Suzuki Y. Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother*. 2000;34(4):427-432.

Miyashita H, Sato T, Tamura T, Tamura O, Tazawa H. The problems of digitalis therapy from the viewpoint of serum concentration with special reference to the sampling time, to the overlapping range of serum concentration where intoxicated and non-intoxicated patients are located and to atrial fibrillation. *Jpn Circ J*. 1986;50(7):628-635.

Moffett BS, Garner A, Zapata T, Orcutt J, Niu M, Lopez KN. Serum digoxin concentrations and clinical signs and symptoms of digoxin toxicity in the paediatric population. *Cardiol Young*. 2016;26(3):493-498.

Moorman JR. Digitalis toxicity at Duke Hospital, 1973 to 1984. *South Med J*. 1985;78(5):561-564.

Mowry JB, Burdmann EA, Anseeuw K, et al; EXTRIP Workgroup. Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Clin Toxicol (Phila)*. 2016;54(2):103-114.

Mutlu M, Aslan Y, Kader Ş, Aktürk-Acar F, Dilber E. Clinical signs and symptoms of toxic serum digoxin levels in neonates. *Turk J Pediatr*. 2019;61(2):244-249.

Nordt SP, Clark RF, Machado C, Cantrell FL. Assessment of digoxin-specific Fab fragment dosages in digoxin poisoning. *Am J Ther*. 2016;23(1):e63-e67.

Table S5 (*Continued*)

References

Odelin MF, Lery N, Delomier Y. Digitalis overdosage: a problem still relevant in the elderly. About 36 cases in a population of 86 cardiac insufficiency in patients in a geriatric unit. Article in French. *J Medecine Legale Droit Medical*. 1986;29(5):445-450.

Ong HT, Ch'ng SL, Masduki A, Chandrasekharan N. Digoxin toxicity: clinical and laboratory assessment. *Med J Malaysia*. 1989;44(4):296-301.

Ordog GJ, Benaron S, Bhasin V, Wasserberger J, Balasubramanium S. Serum digoxin levels and mortality in 5,100 patients. *Ann Emerg Med*. 1987;16(1):32-39.

Park GD, Spector R, Goldberg MJ, Feldman RD. Digoxin toxicity in patients with high serum digoxin concentrations. *Am J Med Sci*. 1987;294(6):423-428.

Pedone C, Corsonello A, Carosella L, Antonelli-Incalzi R; GIFA Investigators. Comparison of digitalis-related adverse events in hospitalized men and women in Italy: an observational study. *Clin Ther*. 2005;27(12):1922-1929.

Piergies AA, Worwag EM, Atkinson AJ Jr. A concurrent audit of high digoxin plasma levels. *Clin Pharmacol Ther*. 1994;55(3):353-358.

Pita-Fernández S, Lombardía-Cortiña M, Orozco-Veltran D, Gil-Guillén V. Clinical manifestations of elderly patients with digitalis intoxication in the emergency department. *Arch Gerontol Geriatr*. 2011;53(2):e106-e110.

Rainey PM. Effects of digoxin immune Fab (ovine) on digoxin immunoassays. *Am J Clin Pathol*. 1989;92(6):779-786.

Sanaei-Zadeh H, Valian Z, Zamani N, Farajidana H, Mostafazadeh B. Clinical features and successful management of suicidal digoxin toxicity without use of digoxin-specific antibody (Fab) fragments—is it possible? *Trop Doct*. 2011;41(2):108-110.

Sánchez de la Rosa R, Rodríguez Hernández N, Cueto Guerreiro T, Rebollo Velázquez A, de Armas Alonso A, Sánchez de la Rosa E. Epidemiologic survey of patients on digoxin treatment. Article in Spanish. *Arch Inst Cardiol Mex*. 1996;66(6):510-518.

Saner HE, Lange HW, Pierach CA, Aeppli DM. Relation between serum digoxin concentration and the electrocardiogram. *Clin Cardiol*. 1988;11(11):752-756.

Savin H, Marcus L, Margel S, Ofarim M, Ravid M. Treatment of adverse digitalis effects by hematoperfusion through columns with antidigoxin antibodies bound to agarose polyacrolein microsphere. *Am Heart J*. 1987;113(5):1078-1084.

Schaeffer TH, Mlynarchek SL, Stanford CF, et al. Treatment of chronically digoxin-poisoned patients with a newer digoxin immune fab—a retrospective study. *J Am Osteopath Assoc*. 2010;110(10):587-592.

Schapel GJ, Hawkins MR, Edwards KDG. A study of serum and myocardial digoxin concentrations in man during cardiac arrest. *Aust N Z J Med*. 1975;5(3):202-210.

See I, Shehab N, Kegler SR, Laskar SR, Budnitz DS. Emergency department visits and hospitalizations for digoxin toxicity: United States, 2005 to 2010. *Circ Heart Fail*. 2014;7(1):28-34.

Shapiro W. Correlative studies of serum digitalis levels and the arrhythmias of digitalis intoxication. *Am J Cardiol*. 1978;41(5):852-859.

Shrager MW. Digitalis intoxication: a review and report of forty cases, with emphasis on etiology. *Arch Intern Med*. 1957;100(6):881-893.

Singh RB, Rai AN, Dube KP, Srivastav DK, Somani PN, Katiyar BC. Radioimmunoassay of serum digoxin in relation to digoxin intoxication. *Br Heart J*. 1975;37(6):619-623.

Singh RB, Singh VP, Vaish SK, Bajpai HS, Dubey KP. Serum digoxin levels in elderly patients in relation to its toxicity. *Indian Heart J*. 1976;28(3):170-173.

Singh RB, Srivastav DK, Mohan M, Dube KP, Katiyar BC. Hypomagnesemia and magnesium sulphate therapy in digoxin intoxication. *Jr Aspo Phys Ind*. 1975;23:367-372.

Singh RB, Vaish SK, Rai AN, Dube KP. Risk factors of digoxin intoxication. *J Indian Med Assoc*. 1975;64(2):36-41.

Smith TW. Review of clinical experience with digoxin immune Fab (ovine). *Am J Emerg Med*. 1991;9(2 suppl 1):1-6.

Smith TW, Butler VP, Haber E, et al. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. *N Engl J Med*. 1982;307(22):1357-1362.

Smith TW, Haber E. Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. *J Clin Invest*. 1970;49(12):2377-2386.

Smolarz A, Abshagen U. Digitalis antibody fragments (Fab) in 90 cases of severe glycoside poisoning. Clinical experiences from a multicentre study. *Herz Kreislauf*. 1986;18(6):261-266.

Smolarz A, Roesch E, Lenz E, Neubert H, Abshagen U. Digoxin specific antibody (Fab) fragments in 34 cases of severe digitalis intoxication. *J Toxicol Clin Toxicol*. 1985;23(4-6):327-340.

Smolarz A, Roesch E, Lenz H. Report of experiences in the treatment of 16 cases of severe glycoside poisoning with digitalis antibody fragments (Fab). Article in German. *Z Kardiol*. 1984;73(2):113-119.

Sonnenblick M, Abraham AS, Meshulam Z, Eylath U. Correlation between manifestations of digoxin toxicity and serum digoxin, calcium, potassium, and magnesium concentrations and arterial pH. *Br Med J (Clin Res Ed)*. 1983;286(6371):1089-1091.

Steiness E. Suppression of renal excretion of digoxin in hypokalemic patients. *Clin Pharmacol Ther*. 1978;23(5):511-514.

Storstein O, Hansteen V, Hatle L, Hillestad L, Storstein L. Studies on digitalis. XIV. Is there any correlation between hypomagnesemia and digitalis intoxication? *Acta Med Scand*. 1977;202(6):445-447.

Sundar S, Burma DP, Vaish SK. Digoxin toxicity and electrolytes: a correlative study. *Acta Cardiol*. 1983;38(2):115-123.

Svaluto Moreolo G, Petrassi S, Del Torso S, Stefanelli U, Da Dalt L, Pellegrino PA. Digitalis toxicity and digoxin blood levels in children. Article in Italian. *G Ital Cardiol*. 1979;9(2):191-196.

Table S5 (*Continued*)

References

Taboulet P. Digitalis intoxication. *Clin Toxicol. Revue du Praticien - Medecine Generale*. 1993;7(217):35-36+39-41.
Tamburrini LR, Curri G, Giudici G, Cafagna D, Gris F, Stefanini P. Digitalis poisoning. Study of the correlations between the serum digoxin level of poisoning and some clinico-functional variables in a sample of 40 poisoned patients. Article in Italian. *Minerva Cardioangiol*. 1980;28(10):667-676.
Tatlisu MA, Ozcan KS, Gungor B, Karatas MB, Zengin A, Nurkalem Z. Inappropriate use of digoxin in patients presenting with digoxin toxicity [abstract OP-143]. *Am J Cardiol*. 2015;115(suppl 1):S62.
Tawakkol AA, Nutter DO, Massumi RA. A prospective study of digitalis toxicity in a large city hospital. *Med Ann Dist Columbia*. 1967;36 (7):402-409.
Tepper D. Frontiers in congestive heart failure: digoxin toxicity: an evaluation in current clinical practice. *Congest Heart Fail*. 1999;5 (1):43.
Ujhelyi MR. Spotlight article: quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. (Mordel A, Halkin H, Zulty I, Almog S, Ezra D. *Clin Pharm Ther*. 1993;53:457-462). *Heart Lung*. 1993;22(6):560-562.
von Arnim T, Krawietz W, Vogt W, Erdmann E. Is the determination of serum digoxin concentration useful for the diagnosis of digitalis toxicity? *Int J Clin Pharmacol Ther Toxicol*. 1980;18(6):261-268.
Wenger TL, Butler VP, Haber E, Smith TW. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. *J Am Coll Cardiol*. 1985;5(5):118A-123A.
Williams P, Aronson J, Sleight P. Is a slow pulse-rate a reliable sign of digitalis toxicity? *Lancet*. 1978;2(8104-8105):1340-1342.
Wofford JL, Hickey AR, Ettinger WH, Furberg CD. Lack of age-related differences in the clinical presentation of digoxin toxicity. *Arch Intern Med*. 1992;152(11):2261-2264.
Woolf AD, Wenger T, Smith TW, Lovejoy FH, Jr. The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med*. 1992;326(26):1739-1744.
Young IS, Goh EM, McKillop UH, Stanford CF, Nicholls DP, Trimble ER. Magnesium status and digoxin toxicity. *Br J Clin Pharmacol*. 1991;32 (6):717-721.

Table S6 Survey 1 Results

Survey Question	Inclusion Criteria Selected
1. Do any of these patient characteristics figure into your decision-making?	• Age • Weight
2. Do any of these concurrent medical conditions figure into your decision-making?	• Acute kidney dysfunction • Atrial fibrillation • Chronic kidney dysfunction (dialysis-dependent) • Chronic kidney dysfunction (dialysis-independent) • Congestive heart failure • Pregnancy status • Thyroid disease
3. Does how the patient is taking digoxin figure into your decision-making?	• Dose • Dosing interval (if chronic) • Time since digoxin dose • Chronicity of use (ie, acute, acute-on-chronic, chronic digoxin toxicity) • Route of administration
4. If the patient is taking any of these concurrent medications, does it figure into your decision-making?	• ACE inhibitors • Antibiotics (macrolides and non-macrolides) • Anticoagulants • Beta blockers • Calcium channel blockers • Diuretics • Herbal supplements • Any heart-rate–controlling medication (especially amiodarone)
5. Do any of these signs or symptoms figure into your decision-making? (Vital signs)	• Blood pressure • Heart rate • Respiration rate
6. Do any of these signs or symptoms figure into your decision-making? (Constitutional makeup)	• Anorexia • Asthenia/fatigue/lethargy • Decreased urine output

Table S6 (*Continued*)

Survey Question	Inclusion Criteria Selected
7. Do any of these signs or symptoms figure into your decision-making? (Neuropsychiatric)	• Coma • Confusion/disorientation • Delirium • Altered mental status • Disturbance of balance • Dizziness • Loss of consciousness/syncope
8. Do any of these signs or symptoms figure into your decision-making? (Gastrointestinal)	• Abdominal pain • Diarrhea • Nausea • Vomiting
9. Do any of these signs or symptoms figure into your decision-making? (Respiratory/cardiovascular)	• Chest tightness • Chest pain • Dyspnea • Shortness of breath • Pulmonary edema
10. Do any of these signs or symptoms figure into your decision-making? (Visual/ocular function)	• Blurred vision • Halos • Change in color discrimination or perception • Decreased visual acuity • Photopsia • Xanthopsia (ie, "yellow" vision)
11. Do any of these laboratory tests figure into your decision-making?	• Blood urea nitrogen • Serum digoxin concentration • Serum calcium concentration • Serum creatinine concentration • Serum lactate concentration • Serum magnesium concentration • Serum potassium concentration • Serum sodium concentration
12. Do any of these additional tests figure into your decision-making?	• Echocardiogram • Electrocardiogram-rate • Electrocardiogram-rhythm • Electrocardiogram-ectopy
13. Using the 5-point Likert scale, please indicate if the following would be important to understand in assessing the literature related to the clinical diagnosis and management of patients with digoxin toxicity.	• Treatments administered • Short-term outcomes • Long-term outcomes
14. Please list anything else that you feel would be important to capture as part of the systematic literature review on the clinical diagnosis and management of patients with digoxin toxicity (optional)	• Role of calcium in management of patients with digoxin toxicity

Table S7. Summary of Evidence-Based Statements for the Clinical Diagnosis and Management of Digoxin Toxicity

Statement Number	Statement	ACC/AHA Grade	Strength of Recommendation/ Endorsement (Summary statistics)
Patient characteristics			
1*	Older age (>70 years) places patients at increased risk of digoxin toxicity even at serum digoxin levels in the "therapeutic range.[1-21]	B-NR	Strong endorsement (M: 8; LQ: 8; DI: 0.13)
Concurrent medical conditions			
2*	Impaired renal function is associated with increased serum digoxin levels.[1,4,5,8,9,13,15-17,19,21-40]	B-NR	Strong endorsement (M: 9; LQ: 8; DI: 0.13)
Digoxin exposure			
3	The nature of the digoxin exposure (acute, acute-on-chronic, chronic), including the most recent time of ingestion, must be evaluated to accurately interpret the serum digoxin levels.[33,41-44]	B-NR	Strong endorsement (M: 9; LQ: 9; DI: 0.00)
Concurrent medications			
4	Clinicians need to consider drug-drug interactions because other medications can increase digoxin levels and/or cause increased sensitivity to the effects of digoxin, even at normal serum digoxin levels.[1,2,7,10,17,22,28,31-33,45-49]	B-NR	Strong endorsement (M: 9; LQ: 8; DI: 0.13)
Signs and symptoms			
5	Symptoms of digoxin toxicity can be nonspecific.[10,25,31,42,44,50-53]	C-LD	Strong endorsement (M: 8.5; LQ: 7.5; DI: 0.13)
6	Heart rate and blood pressure should be considered in the assessment of toxic or life-threatening digoxin exposure.[11,28,31,35,42,45,54]	C-LD	Strong endorsement (M: 8; LQ: 7.5; DI: 0.13)
7	Gastrointestinal fluid loss can exacerbate dehydration, impair glomerular filtration rate (GFR), and alter the intravascular compartment size, which can affect serum digoxin levels.[16,31,55-57]	C-LD	Strong endorsement (M: 8.5; LQ: 7; DI: 0.29)
Serum digoxin concentration			
8*	Serum digoxin concentrations must be measured when evaluating for digoxin toxicity.[2-5,10,23,25,30,38,41,54,58-60]	B-NR	Strong endorsement (M: 8.5; LQ: 8; DI: 0.13)
9*	There is no consistent relationship between serum digoxin concentration and clinical effects.[5,6,11,14,23,30,33,42,43,50,61-64]	B-NR	Strong endorsement (M: 8; LQ: 8; DI: 0.00)
10*	For patients with serum digoxin levels below 3 ng/mL, the diagnosis of digoxin toxicity needs to be taken in clinical context (eg, older age, underlying conduction system disease, impaired renal function).[11,13-16,38,43,50,51,62]	B-NR	Strong endorsement (M: 9; LQ: 8.5; DI: 0.00)
11†	In the absence of other clinical findings, a serum digoxin concentration of X ng/mL is an indication for digoxin Fab therapy in acute ingestions.[11,51]	C-LD	3 ng/mL Weak recommendation against (M: 3; UQ: 5.5; DI: 0.65) 4 ng/mL: No recommendation (DI: 1.04) >4.0 ng/mL Weak endorsement (M: 7; LQ: 3.5; DI: 0.75)
12†	In the absence of other clinical findings, a digoxin concentration of X ng/mL is an indication for digoxin Fab therapy in chronic ingestions.[11,65]	B-NR	3 ng/mL Weak recommendation against (M: 3; UQ: 6; DI: 0.65) 4 ng/mL: No recommendation (DI: 1.04) >4.0 ng/mL Weak endorsement (M: 6.5; LQ: 4.5; DI: 0.75)

Table S7. (*Continued*)

Statement Number	Statement	ACC/AHA Grade	Strength of Recommendation/ Endorsement (Summary statistics)
Serum magnesium concentration			
13	Low magnesium levels are associated with increased sensitivity of the heart to the effects of digoxin.[20,39,44,66-68]	B-NR	Strong endorsement (M: 8.5; LQ: 7; DI: 0.29)
14*	High magnesium levels in adults are associated with acute digoxin toxicity.[66,69]	C-LD	Neutral recommendation (M: 5; DI: 0.52)
15*	Magnesium administration is associated with decreased effects of digoxin on the heart in patients with hypomagnesemia and is a temporizing measure if digoxin Fab is not immediately available.[39]	C-LD	Strong endorsement (M: 8; LQ: 7.5; DI: 0.00)
Serum potassium concentration			
16	Hypokalemia is associated with increased effects of digoxin on the heart.[44,48,56,61,62,70,71]	C-LD	Strong endorsement (M: 8; LQ: 7; DI: 0.29)
17*	High serum potassium can result from acute digoxin toxicity.[8,9,12,22,24,28,34,54,69,72-78]	B-NR	Strong endorsement (M: 9; LQ: 9; DI: 0.00)
18†	In adult patients with acute digoxin ingestion with no other reason for hyperkalemia, serum potassium concentration of X mEq/L would be indication for digoxin Fab therapy.[24,35,79]	C-LD	5 mEq/L: No recommendation (DI: 1.56) 5.5 mEq/L: No recommendation (DI: 1.61) ≥6 mEq/L: Strong endorsement (M: 8; LQ: 6.5; DI: 0.29)
19†	In adult patients on chronic digoxin therapy that have signs or symptoms of digoxin toxicity with no other reason for hyperkalemia, serum potassium concentration of X mEq/L would be indication for digoxin Fab therapy.[24,79]	C-LD	5 mEq/L: No recommendation (DI: 1.56) 5.5 mEq/L: No recommendation (DI: 1.61) ≥6 mEq/L: Strong endorsement (M: 8; LQ:6; DI: 0.29)
Echocardiographic and electrocardiographic findings			
20	Echocardiogram evaluation should be part of the assessment of digoxin toxicity.		No recommendation (DI: 1.56)
21	Electrocardiographic findings can be nonspecific in a patient with digoxin toxicity.[12,21,49,51,52,61,80,81]	B-NR	Strong endorsement (M: 9; LQ: 7; DI: 0.29)
22	Heart rhythm abnormalities, including bradycardia/atrioventricular block and some tachyarrhythmias (eg, paroxysmal atrial tachycardia [PAT] with block) are associated with digoxin toxicity.[3,6-10,15,16,18,23,24,26,28-31,33-35,42,45,48,50,54,57-60,63,69,72,74,76-78,80,82-86]	B-NR	Strong endorsement (M: 9; LQ: 8; DI: 0.13)
Treatment for digoxin toxicity, short- and long-term outcomes			
23*	Activated charcoal is effective in shortening the elimination half-life of digoxin in cases of acute ingestion.[12]	C-LD	Strong endorsement (M: 8; LQ: 7; DI: 0.16)
24	Management of and triggers for digoxin Fab use differ based on the chronicity of toxicity (acute or chronic).[9,28,41,53,77,87]	C-LD	Strong endorsement (M: 8.5; LQ: 7.5; DI: 0.13)
25	Selection of digoxin Fab dosing should follow FDA-approved language as outlined in the digoxin Fab product guide.[17,53,77,87,88]	B-NR	Neutral recommendation (M: 5.5; DI: 0.97)
26	Digoxin Fab is first-line treatment for life-threatening digoxin exposure.[9,35,45,72,78,79,89-93]	B-NR	Strong endorsement (M: 9; LQ: 7.5; DI: 0.13)
27	Digoxin-associated bradyarrhythmia should be treated antidotally rather than with a temporary transvenous pacemaker.[92]	C-LD	Strong endorsement (M: 7.5; LQ: 6.5; DI: 0.29)
28	Digoxin Fab antidotal treatment decreases incidence of death with life-threatening digoxin toxicity.[35,45,72,94,95]	B-NR	Strong endorsement (M: 8; LQ: 8; DI: 0.13)
29	Digoxin Fab antidotal therapy for digoxin toxicity may decrease total medical costs.[24,44,65,95]	B-NR	Strong endorsement (M: 7.5; LQ: 6.5; DI: 0.16)

Table S7. (*Continued*)

Statement Number	Statement	ACC/AHA Grade	Strength of Recommendation/ Endorsement (Summary statistics)
30	Digoxin maintenance therapy should not be restarted in the acute setting following a presentation with digoxin toxicity that required digoxin Fab antidotal treatment, except in rare circumstances and after risk-benefit assessment.[8]	C-LD	Strong endorsement (M: 8; LQ: 7; DI: 0.29)
31	Reoccurrence of acute heart failure symptoms is unlikely to occur after antidotal therapy with digoxin Fab.[72]	B-NR	Strong endorsement (M: 8; LQ: 6.5; DI: 0.16)
Role of calcium in the management of patients with digoxin toxicity			
32	Intravenous calcium is not helpful in the treatment of digoxin-induced hyperkalemia.[36,75]	C-LD	Strong endorsement (M: 8; LQ: 6; DI: 0.29)
33	Intravenous calcium may be harmful in the treatment of the cardiac effects of digoxin.[75]	C-LD	Weak endorsement (M: 7; LQ: 4.5; DI: 0.75)

The quality of the available evidence supporting each statement was determined using the ACC/AHA Task Force in Clinical Practice Guidelines methodology. (B-NR: Level B nonrandomized; C-LD: Level C limited data). The strength of recommendation is based on consensus obtained from the modified Delphi process. Summary statistics for the voting results include median (M), lower quartile (LQ), upper quartile (UQ), and disagreement index (DI). The RAND/UCLA Appropriateness method was used to quantify the levels of disagreement among the voting results.

*Statements revised based on feedback from panelists during Survey 2 and included in Survey 3. Only revised statements from Survey 3, summary statistics, and recommendations based on this survey are included in this table.

†Multi-option survey questions: recommendation and voting results summary statistics for each option have been included.

References

1. Carosella L, Pahor M, Pedone C, et al. Digitalis in the treatment of heart failure in the elderly. The GIFA study results. *Arch Gerontol Geriatr.* 1996;23(3):299-311.
2. Chan AL, Wang MT, Su CY, Tsai FH. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: a population-based study. *Eur J Clin Pharmacol.* 2009;65(12):1237-1243.
3. Charfi R, Ben Sassi M, Gaies E, et al. Digoxin therapeutic drug monitoring: age influence and adverse events. *Tunis Med.* 2020;98(1):35-40.
4. Cobo Sacristan S, Leiva Badosa E, Miquel Zurita ME, et al. Analysis of patients with digoxin intoxication admitted to hospital as emergencies [abstract]. *Eur J Hosp Pharm.* 2014;21:A139.
5. Doering W, König E, Sturm W. Digitalisintoxikation: wertigkeit klinischer und elektrokardiographischer befunde im vergleich zur digoxinkonzentration im serum 2. teil: Patienten mit klinischen hinweisen für eine digitalisintoxikation [Digitalis intoxication: specifity and significance of cardiac and extracardiac symptoms. Part II. Patients with extracardiac symptoms of digitalis intoxications] [Article in German]. *Z Kardiol.* 1977;66(3):129-137.
6. Evered DC, Chapman C. Plasma digoxin concentrations and digoxin toxicity in hospital patients. *Br Heart J.* 1971;33 (4):540-545.
7. Gotsman MS, Schrire V. Toxicity—a frequent complication of digitalis therapy. *S Afr Med J.* 1966;40(25):590-592.
8. Hauptman PJ, Blume SW, Lewis EF, Ward S. Digoxin toxicity and use of digoxin inmmune fab: insights from a national hospital database. *JACC: Heart Failure.* 2016;4(5):357-364.
9. Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin Immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol.* 1991;17(3):590-598.
10. Kirilmaz B, Saygi S, Gungor H, et al. Digoxin intoxication: an old enemy in modern era. *J Geriatr Cardiol.* 2012;9 (3):237-242.
11. Lecointre K, Pisanté L, Fauvelle F, Mazouz S. Digoxin toxicity evaluation in clinical practice with pharmacokinetic correlations. *Clin Drug Invest.* 2001;21(3):225-232.
12. Limon G, Ersoy G, Oray NC, et al. Retrospective evaluation of patients with elevated digoxin levels at an emergency department. *Turk J Emerg Med.* 2016;16(1):17-21.
13. Marik PE, Fromm L. A case series of hospitalized patients with elevated digoxin levels. *Am J Med.* 1998;105(2):110-115.
14. Miura T, Kojima R, Sugiura Y, et al. Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother.* 2000;34 (4):427-432.
15. Moorman JR. Digitalis toxicity at Duke Hospital, 1973 to 1984. *South Med J.* 1985;78(5):561-564.
16. Pita-Fernandez S, Lombardia-Cortina M, Orozco-Veltran D, Gil-Guillen V. Clinical manifestations of elderly patients with digitalis intoxication in the emergency department. *Arch Gerontol Geriatr.* 2011;53(2):e106-e110.
17. Schaeffer TH, Mlynarchek SL, Stanford CF, et al. Treatment of chronically digoxin-poisoned patients with a newer digoxin immune fab–a retrospective study. *J Am Osteopath Assoc.* 2010;110(10):587-592.

18. Shrager MW. Digitalis intoxication: a review and report of forty cases, with emphasis on etiology. *Arch Intern Med.* 1957;100(6):881-893.
19. Singh RB, Vaish SK, Rai AN, Dube KP. Risk factors of digoxin intoxication. *J Indian Med Assoc.* 1975;64(2):36-41.
20. Singh RB, Singh VP, Vaish SK, et al. Serum digoxin levels in elderly patients in relation to its toxicity. *Indian Heart J.* 1976;28(3):170-173.
21. Smith TW, Haber E. Digoxin intoxication: the relationship of clinical preentation to serum digoxin concentration. *J Clin Invest.* 1970;49:2377-2386.
22. Arbabian H, Lee HM, Graudins A. Elderly patients with suspected chronic digoxin toxicity: a comparison of clinical characteristics of patients receiving and not receiving digoxin-Fab. *Emerg Med Australas.* 2018;30(2):242-248.
23. Beller GA, Smith TW, Abelmann WH, et al. Digitalis intoxication. A prospective clinical study with serum level correlations. *N Engl J Med.* 1971;284(18):989-997.
24. Bilbault P, Oubaassine R, Rahmani H, et al. Emergency step-by-step specific immunotherapy in severe digoxin poisoning: an observational cohort study. *Eur J Emerg Med.* 2009;16(3):145-149.
25. Bohmer T, Røseth A. Prolonged digitoxin half-life in very elderly patients. *Age Ageing.* 1998;27(2):222-224.
26. Calypso G, Emmanuel B, Lucie C, et al. Chronic digitalis poisoning treated with anti-digoxin Fab: a critical analysis of treatment indications and patient outcome [abstract P-144]. *Ann Intensive Care.* 2018;8(suppl 1):144.
27. Supervía Caparrós A, Salgado García E, Calpe Perarnau X, et al. Immediate and 30 days mortality in digoxin poisoning cases attended in the Hospital Emergency Services of Catalonia, Spain. *Emergencias.* 2019;31(1):39-42.
28. Chan BS, Isbister GK, Page CB, et al. Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4). *Clin Toxicol (Phila).* 2019;57(7):638-643.
29. Dubnow MH, Burchell HB. A comparison of digitalis intoxication in two separate periods. *Ann Intern Med.* 1965;62:956-965.
30. Jitapunkul S, Kongsawat V, Sutheparak S. Digoxin toxicity in Thai medical patients: clinical manifestations and an appropriate diagnostic serum level. *Southeast Asian J Trop Med Public Health.* 2002;33(3):608-612.
31. Joos HA, Johnson JL. Digitalis intoxication in infancy and childhood. *Pediatrics.* 1957;20(5, Part 1):866-876.
32. Kockova R, Skvaril J, Cernohous M, et al. Five year two center retrospective analysis of patients with toxic digoxin serum concentration. *Int J Cardiol.* 2011;146(3):447-448.
33. Koren G, Parker R. Interpretation of excessive serum concentrations of digoxin in children. *Am J Cardiol.* 1985;55 (9):1210-1214.
34. Lapostolle F, Devallière E, Alhéritière A, Adnet F. Relation between creatinine level and kalaemia in patients with digitalis poisoning [Translated from French]. *Presse Med.* 2012;41(12 pt 1):1297-1299.
35. Lapostolle F, Borron SW, Verdier C, et al. Assessment of digoxin antibody use in patients with elevated serum digoxin following chronic or acute exposure. *Intensive Care Med.* 2008;34(8):1448-1453.
36. Levine M, Nikkanen H, Pallin DJ. The effects of intravenous calcium in patients with digoxin toxicity. *J Emerg Med.* 2011;40(1):41-46.
37. Piergies AA, Worwag EM, Atkinson AJ, Jr. Pharmacoepidemiology and drug utilization: a concurrent audit of high digoxin plasma levels. *Clin Pharmacol Ther.* 1994;55(3):353-358.
38. Schapel GJ, Hawkins MR, Edwards KDG. A study of serum and myocardial digoxin concentrations in man during cardiac arrest. *Aust N Z J Med.* 1975;5(3):202-210.
39. Singh RB, Srivastav DK, Mohan M, et al. Hypomagnesemia and magnesium sulphate therapy in digoxin intoxication. *Jr Aspo Phys Ind.* 1975;22.
40. Wofford JL, Hickey AR, Ettinger WH, Furberg CD. Lack of age-related differences in the clinical presentation of digoxin toxicity. *Arch Intern Med.* 1992;152(11):2261-2264.
41. Chhabra N, Valento M, Bryant SM, Aks SE. Digoxin-specific antibody fragment dosing: a case series. *Am J Ther.* 2015;23(6):e1597-e1601.
42. Howard D, Smith CI, Stewart G, et al. A prospective survey of the incidence of cardiac intoxication with digitalis in patients being admitted to hospital and correlation with serum digoxin levels. *Aust N Z J Med.* 1973;3(3):279-284.
43. Miyashita H, Sato T, Tamura T, et al. The problems of digitalis therapy from the viewpoint of serum concentration with special reference to the sampling time, to the overlapping range of serum concentration where intoxicated and non-intoxicated patients are located and to atrial fibrillation. *Jpn Circ J.* 1986;50(7):628-635.
44. Nordt SP, Clark RF, Machado C, Cantrell FL. Assessment of digoxin-specific fab fragment dosages in digoxin poisoning. *Am J Ther.* 2016;23(1):e63-e67.
45. Chan BS, Isbister GK, Chiew A, et al. Clinical experience with titrating doses of digoxin antibodies in acute digoxin poisoning. (ATOM-6). *Clin Toxicol (Phila).* 2022;60(4):433-439.
46. Gomes T, Mamdani MM, Juurlink DN. Macrolide-induced digoxin toxicity: a population-based study. *Clin Pharmacol Ther.* 2009;86(4):383-386.

47. Ibañez C, Carcas AJ, Frias J, Abad F. Activated charcoal increases digoxin elimination in patients. *Int J Cardiol.* 1995;48 (1):27-30.
48. Jorgensen AW, Sorensen OH. Digitalis intoxication: a comparative study on the incidence of digitalis intoxication during the periods 1950-52 and 1964-6. *Acta Med Scand.* 1970;188(3):179-183.
49. Mordel A, Halkin H, Zulty L, et al. Quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. *Clin Pharmacol Ther.* 1993;22(6):560-562.
50. Boman A. Digitalis intoxication in geriatric in-patients. A prospective clinical study of the value of serum digitalis concentration measurement. *Acta Med Scand.* 1983;214(5):345-351.
51. Lewander WJ, Gaudreault P, Einhorn A, et al. Acute pediatric digoxin ingestion: aA ten-year experience. *Am J Dis Child.* 1986;140(8):770-773.
52. Moffett BS, Garner A, Zapata T, et al. Serum digoxin concentrations and clinical signs and symptoms of digoxin toxicity in the paediatric population. *Cardiol Young.* 2016;26(3):493-498.
53. Park GD, Spector R, Goldberg MJ, Feldman RD. Digoxin toxicity in patients with high serum digoxin concentrations. *Am J Med Sci.* 1987;294(6):423-428.
54. El-Sarnagawy GN, El Sharkawy SI, Helal NE. Predictive factors for recurrence of serious arrhythmias in patients with acute digoxin poisoning. *Cardiovasc Toxicol.* 2021;21(10):835-847.
55. Sonnenblick M, Abraham AS, Meshulam Z, Eylath U. Correlation between manifestations of digoxin toxicity and serum digoxin, calcium, potassium, and magnesium concentrations and arterial pH. *Br Med J.* 1983;286(6371):1089-1091.
56. Steiness E. Suppression of renal excretion of digoxin in hypokalemic patients. *Clin Pharmacol Ther.* 1978;23(5):511-514.
57. Tawakkol AA, Nutter DO, Massumi RA. A prospective study of digitalis toxicity in a large city hospital. *Med Annals District of Columbia.* 1967;36(7):402-409.
58. Abad-Santos FF, Carcas AJ, Ibáñez C, Frías J. Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity. *Ther Drug Monit.* 2000;22(2):163-168.
59. Eraker SA, Sasse L. The serum digoxin test and digoxin toxicity: a Bayesian approach to decision making. *Circulation.* 1981;64(2):409-420.
60. Ordog GJ, Benaron S, Bhasin V, et al. Serum digoxin levels and mortality in 5,100 patients. *Ann Emerg Med.* 1987;16 (1):32-39.
61. Mutlu M, Aslan Y, Kader S, et al. Clinical signs and symptoms of toxic serum digoxin levels in neonates. *Turk J Pediatr.* 2019;61(2):244-249.
62. Ong HT, Ch'ng SL, Masduki A, Chandrasekharan N. Digoxin toxicity: clinical and laboratory assessment. *Med J Malaysia.* 1989;44(4):296-301.
63. Savin H, Marcus L, Margel S, et al. Treatment of adverse digitalis effects by hematoperfusion through columns with anti-digoxin antibodies bound to agarose polyacrolein microsphere. *Am Heart J.* 1987;113(5):1078-1084.
64. Singh RB, Rai AN, Dube KP, et al. Radioimmunoassay of serum digoxin in relation to digoxin intoxication. *Br Heart J.* 1975;37:619-623.
65. DiDomenico RJ, Walton SM, Sanoski CA, Bauman JL. Analysis of the use of digoxin immune fab for the treatment of non-life-threatening digoxin toxicity. *J Cardiovasc Pharmacol Ther.* 2000;5(2):77-85.
66. Beller GA, Hood Jr WB, Smith TW, et al. Correlation of serum magnesium levels and cardiac digitalis intoxication. *Am J Cardiol.* 1974;33(2):225-229.
67. Storstein O, Hansteen V, Hatle L, et al. Studies on digitalis. *Acta Med Scand.* 1977;202(6):445-447.
68. Young IS, Goh EM, McKillop UH, et al. Magnesium status and digoxin toxicity. *Br J Clin Pharmacol.* 1991;32(6):717-721.
69. Gheshlaghi F, Wong A, Dorooshi G, et al. Ten years of experience in treating patients with digoxin toxicity without using digoxin fab antibody. *Int J Med Toxicol Forensic Med.* 2021;11(1):31239.
70. LaFountain N, Marino R, Abesamis M. Evaluating the need for digoxin immune Fab (ovine) therapy in chronic digoxin toxicity. *J Med Toxicol.* 2019;15:72.
71. Sundar S, Burma DP, Vaish SK. Digoxin toxicity and electrolytes: a correlative study. *Acta Cardiologica.* 1983;38 (2):115-123.
72. Antman EM, Wenger TL, Butler Jr VP, et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation.* 1990;81(6):1744-1752.
73. Bismuth C, Gaultier M, Conso F, Efthymiou ML. Hyperkalemia in acute digitalis poisoning: prognostic significance and therapeutic implications. *Clin Toxicol.* 1973;6(2):153-162.
74. Dally S, Bismuth C, Alperovitch A, et al. Facteurs pronostiques de l'intoxication digitalique aiguë [Prognostic factors in acute digitalis poisoning] [Article in French]. *Schweiz Med Wochenschr.* 1982;112(31-32):1113-1116.
75. Farrell N, Hack J. Lady stone heart? *J Med Toxicol.* 2017;13(1):33.

76. Gaultier M, Fournier E, Efthymiou ML, et al. Intoxication digitalique aiguë (70 observations) [Acute digitalis poisoning (70 cases)] [Article in French]. *Bull Mem Soc Med Hop Paris.* 1968;119(3):247-274.
77. Manini AF, Nelson LS, Hoffman RS. Prognostic utility of serum potassium in chronic digoxin toxicity: a case-control study. *Am J Cardiovasc Drugs.* 2011;11(3):173-178.
78. Woolf AD, Wenger T, Smith TW, Lovejoy FH, Jr. . The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med.* 1992;326(26):1739-1744.
79. Al Lawati I, Cormier M, Gosselin S. Variability of international clinical toxicologists recommendations concerning the use of digoxin-specific antibody fragments [abstract]. *Clin Toxicol.* 2017;55(7):708-709.
80. Lely AH, van Enter CH. Large-scale digitoxin intoxication. *Br Med J.* 1970;3(5725):737-740.
81. Williams P, Aronson J, Sleight P. Is a slow pulse-rate a reliable sign of digitalis toxicity? *The Lancet.* 1978;2(8104-8105):1340-1342.
82. Chan BSH, Chiew AL, Page CB, et al. Acute digoxin overdose and response to antibody (DORA study). *Clin Toxicol.* 2017:378.
83. Chen JY, Liu PY, Chen JH, Lin LJ. Safety of transvenous temporary cardiac pacing in patients with accidental digoxin overdose and symptomatic bradycardia. *Cardiology.* 2004;102(3):152-155.
84. Detweiler DK, Trautvetter E. Ein EKG-punktsystem zur erkennung von digoxin- bzw. digitalisintoxikationen [ECG scoring system for detection of digitoxin or digitalis poisoning] [Article in German]. *Berl Munch Tierarztl Wochenschr.* 1980;93(21):424-426.
85. Sanaei-Zadeh H, Valian Z, Zamani N, et al. Clinical features and successful management of suicidal digoxin toxicity without use of digoxin-specific antibody (Fab) fragments–is it possible? *Trop Doct.* 2011;41(2):108-110.
86. Saner HE, Lange HW, Pierach CA, Aeppli DM. Relation between serum digoxin concentration and the electrocardiogram. *Clin Cardiol.* 1988;11(11):752-756.
87. Mowry JB, Burdmann EA, Anseeuw K, et al. Extracorporeal treatment for digoxin poisoning: Systematic review and recommendations from the extrip workgroup. *Clin Toxicol (Phila).* 2016;54(2):103-114.
88. Listiawan M, Lackey G, Alsop J, et al. A 10 year retrospective review of digoxin immune Fab use in digoxin exposures. *Clinical Toxicology.* 2012;50(7):574-720.
89. Smith TW, Butler VP, Haber E, et al. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. *N Engl J Med.* 1982;307(22):1357-1362.
90. Smith TW. Review of clinical experience with digoxin immune Fab (ovine). *Am J Emerg Med.* 1991;9(2):1-6.
91. Smolarz A, Roesch E, Lenz E, et al. Digoxin specific antibody (Fab) fragments in 34 cases of severe digitalis intoxication. *Clin Toxicol.* 1985;23(4-6):327-340.
92. Taboulet P, Baud FJ, Bismuth C, Vicaut E. Acute digitalis intoxication–is pacing still appropriate? *Clin Toxicol.* 1993;31(2):261-273.
93. Wenger TL, Butler VP, Haber E, Smith TW. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. *J Am Coll Cardiol.* 1985;5(5):118A-123A.
94. Lapostolle F, Borron SW, Verdier C, et al. Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med.* 2008;36(11):3014-3018.
95. Mauskopf JA, Wenger TL. Cost-effectiveness analysis of the use of digoxin immune Fab (ovine) for treatment of digoxin toxicity. *Am J Cardiol.* 1991;68(17):1709-1714.