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Expert Consensus on the Diagnosis and Management of Digoxin Toxicity

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Author contributions:

JBH: conceptualization, formal analysis, methodology, project administration, writing- original draft, review & editing

SW: methodology, writing- original draft, review & editing

RZ: methodology, writing- review & editing

MWR: formal analysis, writing- review & editing

PJH: conceptualization, formal analysis, methodology, project administration, supervision, writing- original draft, review & editing

Systematic literature review: JBH and PJH, screening for relevance

SW and RZ: extraction of data and level of evidence.

All authors had access to the data.

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CLINICAL SIGNFICANCE (65 words)

- Assessment for 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.

ABSTRACT (171 words)

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 (i.e. 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.

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, 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.

METHODS

This project used an SLR and modified Delphi process (**Figure 1**) that involved a series of surveys. Participants included 4 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 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 (i.e. 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 (i.e. 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

(i.e. 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 (i.e. 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 (i.e. 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 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 (i.e. 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 (i.e. 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 (i.e. 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 (e.g. 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 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 (i.e. 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 (i.e., 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 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-dig 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.

FIGURE LEGENDS

Figure 1 The modified Delphi process.

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

Figure 2 PRISMA flow diagram**.**

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure S1 Studies included by year (n=114)

Figure 1

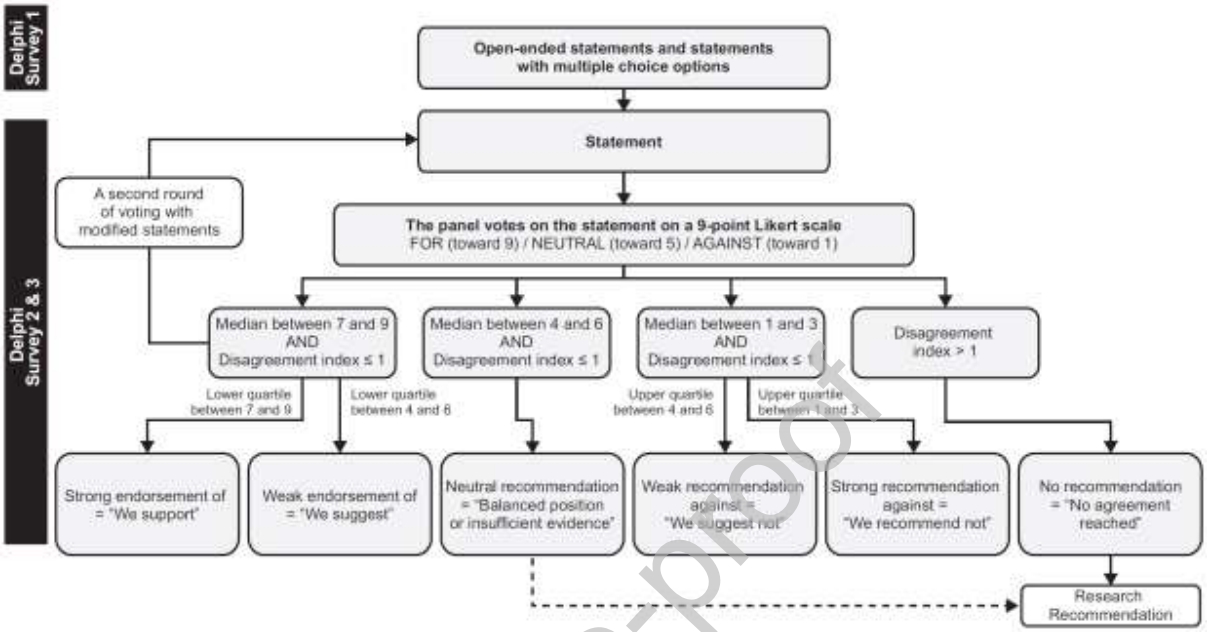
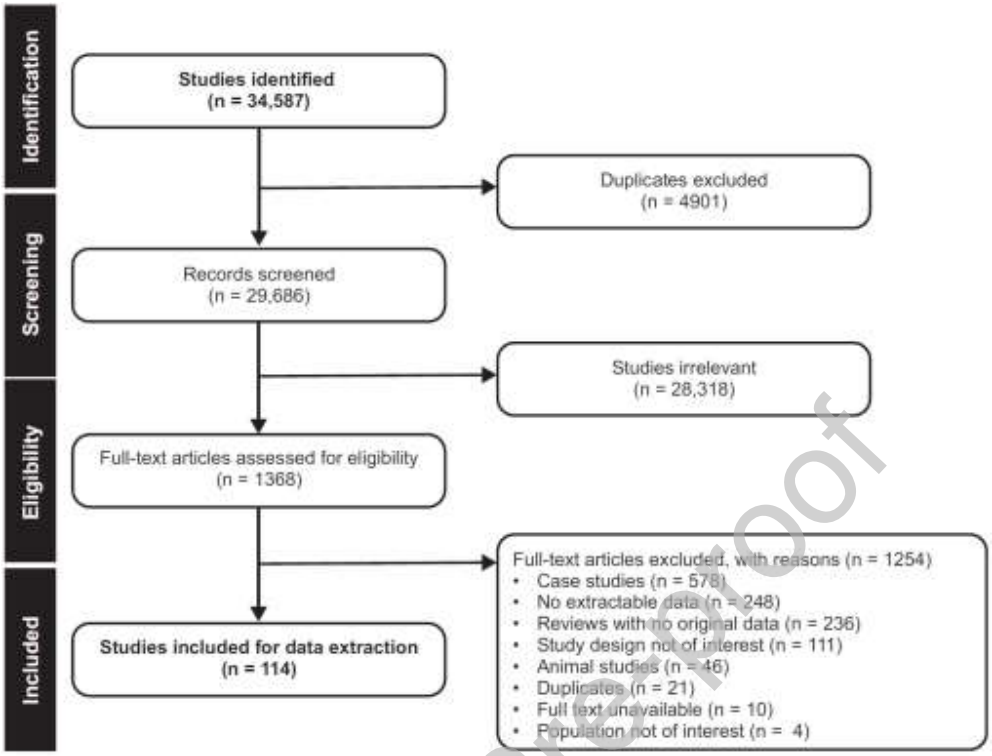


Figure 2



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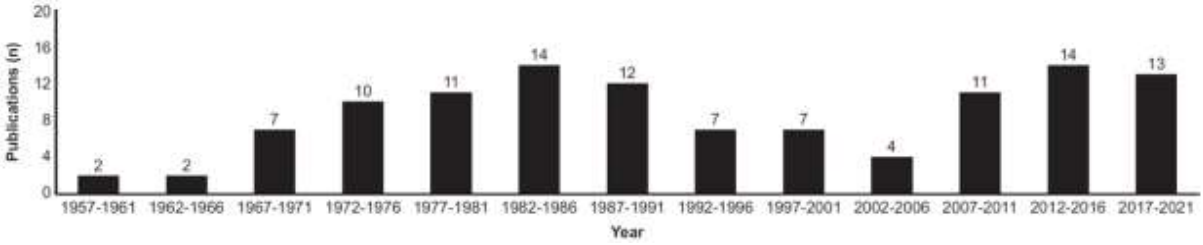

Table 1. Definitions

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

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 (e.g., 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	<u>3 ng/mL</u> Weak recommendation against (M: 3; UQ: 5.5; DI: 0.65) <u>4 ng/mL:</u> No recommendation (DI: 1.04) <u>>4.0 ng/mL</u> 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	<u>3 ng/mL</u> Weak recommendation against (M: 3; UQ: 6; DI: 0.65) <u>4 ng/mL:</u> No recommendation (DI: 1.04) <u>>4.0 ng/mL</u> Weak endorsement (M: 6.5; LQ: 4.5; DI: 0.75)
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	<u>5 mEq/L:</u> No recommendation (DI: 1.56) <u>5.5 mEq/L:</u> No recommendation (DI: 1.61) <u>≥6 mEq/L:</u> 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	<u>5 mEq/L:</u> No recommendation (DI: 1.56) <u>5.5 mEq/L:</u> No recommendation (DI: 1.61) <u>≥6 mEq/L:</u> 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 (e.g., 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)
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.

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 (a) in the setting of life-threatening digoxin exposure to decrease the likelihood of death; (b) 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; (c) 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 (d) 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

Table S1

	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) 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
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 (e.g. non-digoxin, or non-digitalis) cardiac glycosides (i.e. 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 about a case report, is it unusual and interesting?	

*1995 to present; first 250 hits.

LILACS = 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

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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
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

Supplemental 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 (e.g., 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	<u>3 ng/mL</u> Weak recommendation against (M: 3; UQ: 5.5; DI: 0.65) <u>4 ng/mL:</u> No recommendation (DI: 1.04) <u>>4.0 ng/mL</u> 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	<u>3 ng/mL</u> Weak recommendation against (M: 3; UQ: 6; DI: 0.65) <u>4 ng/mL:</u>

			No recommendation (DI: 1.04) <u>>4.0 ng/mL</u> Weak endorsement (M: 6.5; LQ: 4.5; DI: 0.75)
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	<u>5 mEq/L:</u> No recommendation (DI: 1.56) <u>5.5 mEq/L:</u> No recommendation (DI: 1.61) <u>≥6 mEq/L:</u> 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 (e.g., 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)
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.

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