Diagnosis and practical management of digoxin toxicity: a narrative review and consensus

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There are currently no universally accepted guidelines for the management of digoxin toxicity. In the absence of clinical practice guidelines, a set of consensus recommendations for management of digoxin toxicity in the clinical setting were developed through a modified Delphi approach. The recommendations highlight the importance of early recognition of signs of potentially life-threatening toxicity that requires immediate treatment with digoxin-specific antibodies. The consensus identifies a straightforward approach to dosing immune antibody fragments according to the presence or absence of signs of life-threatening toxicity. Supportive measures and management of specific signs of toxicity are also covered. *European Journal of Emergency Medicine* 30: 395–401 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

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Background

Cardiac glycosides are some of the oldest medications that remain in contemporary therapeutic use. For common cardiac disorders such as atrial fibrillation and heart failure, digoxin does not have a significant impact on mortality but has been shown in randomised controlled trials to reduce hospital admissions and improve patient well-being [1,2].

Although digoxin has a narrow therapeutic window, toxicity is an uncommon occurrence particularly now that low-dose regimens are standard in clinical practice. However, careful consideration and monitoring is needed in all patients to avoid rare, potentially life-threatening events. Healthcare professionals need to be able to identify patients at risk of developing digoxin toxicity, recognise toxicity quickly if it develops, and act promptly with appropriate interventions.

Using clinical experience and the limited evidence available in the literature, a consensus on the management of digoxin toxicity in adults was reached.

Methods

A group of physicians with experience in the management of digoxin toxicity was convened (see Table, Supplemental digital content 1, *http://links.lww.com/EJEM/A394*).

Consensus statements were developed using a variation of the Delphi method (estimate-talk-estimate) in which participants were allowed to interact between iterations of the statements. Comments and scoring were not anonymized so that multi-speciality input was visible at each stage. Based on a review of the literature, a preliminary set of statements was prepared and sent to the panel as an online questionnaire. For each statement, participants were asked to indicate whether the statement should be retained or deleted and to provide their qualitative feedback.

The list of statements was revised and re-circulated via an online questionnaire. In the second round of review, participants were asked to provide quantitative feedback, rating their agreement with each statement on a scale of 1 (strongly disagree) to 10 (strongly agree). There was also the opportunity to include comments alongside the quantitative ratings.

The feedback from the second round of review was incorporated into a revised set of statements, which were then discussed in a videoconference attended by all of the authors. Based on the discussions, a final set of statements was prepared and circulated to the group for review and approval.

Results

The final set of statements on which the panel reached consensus is presented in Table 1 (Diagnosis and investigation) and Table 2 (Management).

Diagnosis of digoxin toxicity

Diagnosis is based primarily on clinical suspicion and clinical features including electrocardiographic (ECG)

Table 1 Consensus statements on diagnosis and investigation of digoxin toxicity

Presentation and diagnosis

- The diagnosis of digoxin toxicity is based primarily on clinical suspicion and clinical features (including ECG changes) suggestive of digoxin intoxication, and can be confirmed by assessment of serum digoxin levels.
- Digoxin toxicity can occur as a result of acute, chronic or acute-on-chronic over-ingestion; most cases involve chronic toxicity in the setting of deteriorating renal function.
- Serum digoxin levels do not correlate consistently with toxicity; consequently, digoxin levels should be interpreted cautiously when considering the diagnosis of digoxin toxicity.
- Digoxin toxicity predominantly affects the elderly and risk factors include renal impairment, electrolyte imbalances (hypokalaemia, hypomagnesaemia, hypercalcaemia) and dehydration.
- Interactions between digoxin and other drugs (including calcium channel blockers, non-steroidal anti-inflammatory drugs, diuretics, macrolide antibiotics) are possible and may increase the risk of digoxin toxicity in particular patient groups.
- Symptoms of digoxin toxicity include gastrointestinal (loss of appetite, nausea, vomiting, diarrhoea), neurological (headache, confusion, lethargy), visual (blurring, halos and occasionally alterations in colour perception) and cardiac (arrhythmia, often associated with fatigue) disturbances.
- Cardiac toxicity is the leading cause for concern and can include a broad range of arrhythmias including bradycardia, all degrees of atrioventricular block, premature ventricular contractions and ventricular tachycardia, as well as hypotension and cardiogenic shock.

Assessments and investigations

- For all patients with suspected digoxin toxicity, general and cardiac health status should be assessed as well as concomitant therapy and recent intercurrent illnesses.
- Distribution of ingested digoxin to tissues takes several hours and accurate measurement of serum digoxin levels requires at least 6 h to have passed from the last ingestion; therefore, management of acute toxicity should not be delayed while waiting for measurements of digoxin concentrations.
- In the absence of clinical signs, serum digoxin levels should be re-evaluated at an appropriate time-point after last ingestion for accurate assessment of potential toxicity.
- Renal function should be assessed and monitored in all patients presenting with suspected digoxin toxicity: digoxin is eliminated primarily by the kidneys.
- Serum electrolytes should be measured: hypokalaemia, hypercalcaemia and hypomagnesaemia can exacerbate the effects of digoxin toxicity.
- All patients should be monitored with serial electrocardiograms (ECGs).
  - Typical features of digoxin toxicity include arrhythmias, ST segment depression ('scooped out' appearance), T wave flattening and increased U wave amplitude.
  - ECG changes may occur in individuals receiving digoxin but without digoxin toxicity.
- Continuous cardiac monitoring should be offered, if available, especially if ECG disturbances are present.

Table 2 Consensus statements on management of digoxin toxicity

Use of digoxin immune antibody fragments

- Digoxin immune Fab (DigiFab) is the mainstay of treatment for life-threatening digoxin toxicity.
- Signs of potentially life-threatening digoxin toxicity that require immediate treatment with digoxin immune Fab include:
  - Ventricular tachycardia or fibrillation
  - Asystole or symptomatic high-degree atrioventricular block
  - Serum potassium >6.5 mmol/L
  - Hypotension associated with end-organ dysfunction.
- For patients with potentially life-threatening digoxin toxicity who are in cardiac arrest, five vials (or as many vials as available up to a maximum of five) of digoxin immune Fab (40 milligrams per vial) should be administered immediately; if an adequate clinical response is not seen after 30 min, a further five vials can be given. For other cases of life-threatening digoxin toxicity, an initial dose of 1–2 vials may be administered immediately and repeated based on clinical response.
- In cases of digoxin toxicity without life-threatening signs, digoxin immune Fab is appropriate for selected patients (including those with very high serum digoxin levels or elevated digoxin levels and troublesome toxicity) after the assessment of serum digoxin levels.
  - The dose given should be half that required to achieve full neutralisation of digoxin and can be calculated as: *serum digoxin concentration (nanograms/ml or micrograms/L) × weight (kg) × 0.005*; the dose should be rounded up to the nearest full vial.
  - Patients should be monitored closely after administration of digoxin immune Fab, including assessment of serum potassium concentrations, body temperature, blood pressure, ECG and renal function (serum urea and creatinine and estimated glomerular filtration rate); monitoring should continue until potassium concentration, ECG and renal function are 'normalised'.
- Treatment with digoxin immune Fab may lead to loss of therapeutic activity of digoxin, and could theoretically exacerbate heart failure or rapid ventricular response in atrial fibrillation. After toxicity has resolved, digoxin may need to be reinitiated or alternative therapy introduced. If digoxin is reinitiated, the timing of reinitiation and the dose required will require careful consideration.
- Adverse events may occur up to 14 days after the administration of digoxin immune Fab; late adverse events are uncommon and should be reported to appropriate authorities.

Other treatment options

- Mild digoxin toxicity (i.e. mild symptoms without ECG changes or arrhythmia) associated with chronic over-ingestion can generally be managed by stopping digoxin or reducing the digoxin dose.
- After other management, including use of digoxin immune Fab, treatment with activated charcoal may be considered within 2 h of ingestion in cases of acute digoxin overdose.
- Due to the large volume of distribution of digoxin and relatively high protein binding, treatment to enhance digoxin elimination (e.g. dialysis, haemoperfusion) is not generally recommended.
- Severe hypokalaemia (serum potassium <2.5 mmol/L) can be managed with additional potassium, taking care to avoid rebound hyperkalaemia.
- Mild-to-moderate hyperkalaemia (serum potassium 5.5–6.5 mmol/L) should resolve with digoxin immune Fab treatment.
- If digoxin immune Fab is not immediately available, ventricular tachyarrhythmias can be treated with lidocaine or magnesium sulfate.
- Bradyarrhythmias can be treated with atropine, but drugs such as adrenaline and isoprenaline should be avoided as they can trigger ventricular fibrillation; cardiac pacing may be needed for some patients, but should only be undertaken by expert teams.

Other management considerations

- Hospital emergency departments should have rapid access (ideally within 1 h) to stocks of at least five vials of digoxin immune Fab.
- Treatment for digoxin toxicity should be initiated by the first medical contact (e.g. emergency physician, intensive care physician or cardiologist); subsequent care may require input of an interdisciplinary team with expertise in toxicology and intensive care.

changes suggestive of digoxin intoxication. Most cases involve chronic over-ingestion and develop insidiously [3,4].

Symptoms of digoxin toxicity are mostly non-specific in nature and include gastrointestinal and neurological disturbances. Visual disturbances are more characteristic of digoxin toxicity.

Digoxin toxicity can result in a broad range of arrhythmias including bradycardia and tachycardia (none of which are specific to digoxin toxicity) [5–7]. Signs of life-threatening digoxin toxicity include:

(1) Ventricular tachycardia or fibrillation;
(2) Asystole, symptomatic high-degree atrioventricular block or atropine-resistant bradycardia;
(3) Severe hyperkalaemia (serum potassium >6.5 mmol/L);
(4) Hypotension associated with end-organ dysfunction.

Serum digoxin levels do not reliably correlate with toxicity, which can occur even at levels normally regarded as within the therapeutic range (0.8–2.0 ng/ml, with a narrower range of 0.5–0.8 ng/ml increasingly favoured in heart failure) [8].

Risk factors for digoxin toxicity

Various factors are associated with an increased risk of toxicity occurring during chronic digoxin treatment (Table 3) [9]. Most cases of digoxin toxicity occur in older individuals receiving chronic digoxin therapy and against a background of deteriorating renal function. Interactions between digoxin and other drugs are possible.

Assessments and investigations
General health status

General and cardiac health status as well as concomitant therapy and recent intercurrent illnesses should be assessed for all patients who present with suspected digoxin toxicity.

Serum digoxin measurement

Complete distribution of digoxin to tissues takes several hours and serum digoxin levels in the first few hours after dosing are not reflective of either therapeutic activity or potential toxicity. Consequently, at least 6 h and ideally 8–12 h should be allowed between the last dose of digoxin and measurement of serum digoxin levels to indicate the severity of intoxication. Nevertheless, an initial measurement of digoxin levels should be carried out at the time when overdose is suspected. Treatment of life-threatening digoxin toxicity should not be delayed while waiting for the results of serum digoxin measurements.

Most digitalis immunoassays do not distinguish between free and bound digoxin. Hence digoxin levels can be misleading in patients treated with digoxin immune Fab during the time it takes for this to be cleared completely from the body (variable, but can be up to 3 weeks) [10].

Serum digoxin measurements can be of value in assessing potential toxicity in cases where digoxin intoxication is suspected but clinical or ECG signs of toxicity are absent. For the reasons described above, at least 6 h should have elapsed after the last dose of digoxin before measuring serum digoxin.

Table 3   Factors associated with an increased risk of digoxin toxicity

• Advanced age
• Hypokalaemia
• Hypomagnesaemia
• Hypercalcaemia
• Renal insufficiency
• Dehydration
• Hypoxaemia
• Myocardial ischaemia

Renal function and electrolytes

Digoxin is eliminated primarily in the urine and many cases of chronic digoxin toxicity occur in the context of declining renal function. Renal function should be assessed and monitored in all patients presenting with suspected digoxin toxicity.

Hyperkalaemia is an indicator of disease severity, particularly in cases of acute digoxin toxicity. At the same time, acute or chronic hypokalaemia [11], hypomagnesaemia [12] and hypercalcaemia [13] can increase the potential for toxicity. Therefore, serum electrolytes should be monitored regularly.

Cardiac monitoring

Electrocardiogram monitoring is essential for all patients with suspected toxicity. In addition to the arrhythmias considered above, changes on the ECG typical of digoxin toxicity can include down-sloping ST segment depression ('scooped out' or 'reverse tick' appearance), flattened/inverted T waves and increased U wave amplitude. However, all these changes can also be seen in patients receiving digoxin without toxicity. Continuous cardiac monitoring should be offered, where available, particularly for patients with ECG disturbances.
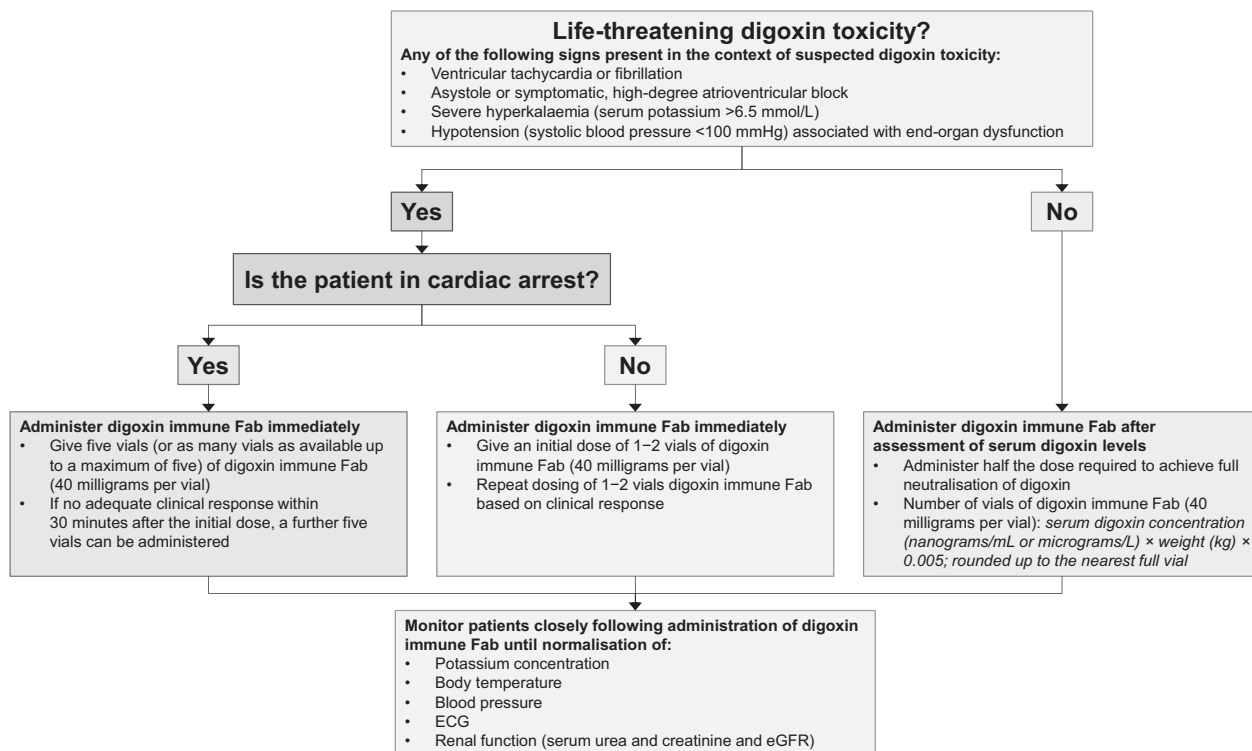
Management of digoxin toxicity
Use of digoxin immune Fab for life-threatening toxicity

Treatment should be initiated immediately by the first medical contact, which may be an emergency or acute medicine physician, intensive care physician or cardiologist depending on the setting. Subsequent care may require input from an interdisciplinary team with expertise in toxicology and intensive care. Withdrawing digoxin can have an impact on the underlying management of the patient's atrial fibrillation and/or heart failure and so early involvement of cardiologists is advisable.

Digoxin immune antibody fragments (digoxin immune Fab, DigiFab, Protherics Medicines Developments Ltd) should be initiated immediately in patients with signs of life-threatening toxicity (**Fig. 1**). Response rates in the range of 50–90% have been reported following digoxin immune Fab treatment in prospective [14,15] and observational studies [16–18], with rapid resolution of toxicity [15,19–21]. Non-significant trends to reduced in-hospital mortality and early rehospitalisation were observed in a recent retrospective analysis [22].

The consensus expert opinion was that for patients with digoxin toxicity in cardiac arrest (loss of cardiac output due to asystole, pulseless electrical activity or tachyarrhythmias), five vials of digoxin immune Fab (40 milligrams per vial) are administered immediately. If five vials are not immediately accessible, as many vials as available up to the maximum of five should be given. If there is not an adequate clinical response after the initial dose of digoxin immune Fab, a further five vials can be administered.

Fig. 1

Guidelines for treatment of digoxin toxicity with digoxin immune Fab.

For all other cases of life-threatening digoxin toxicity (i.e. patients not in cardiac arrest), an initial dose of 1–2 vials should be sufficient for neutralisation of digoxin toxicity in most cases, and can be followed with incremental doses of 1–2 vials, until resolution of toxicity. Expert advice should be sought for patients who have ingested very large amounts of digoxin and in cases of ongoing toxicity after administration of digoxin immune Fab.

Potential use of digoxin immune Fab in absence of life-threatening signs

Administration of digoxin immune Fab is also sometimes appropriate for selected patients without life-threatening signs. This includes both asymptomatic patients and patients with non-life-threatening signs of toxicity and with very high serum digoxin (>12 nanograms/ml). Use of digoxin immune Fab is also appropriate following serum digoxin measurement for patients with less elevated serum digoxin levels when associated with troublesome toxicity (e.g. moderate to severe gastrointestinal symptoms or bradycardia without high-degree atrioventricular block). In such cases, the number of vials of digoxin immune Fab given should be based on the measured serum digoxin level using the formula provided in Table 1 and Fig. 1 (calculated as half that required to achieve full neutralisation of digoxin). Half the full neutralisation dose is recommended in these patients as full neutralisation may not be required to achieve adequate symptom relief and could also adversely affect patients who are dependent on the therapeutic actions of digoxin.

Monitoring and adverse effects

Hypokalaemia associated with digoxin immune Fab administration generally resolves spontaneously within several hours, but potassium levels should be assessed regularly, particularly during the first 6 h following treatment. The reduction in free digoxin following treatment with digoxin immune Fab may lead not only to a reduction in digoxin-induced toxicity but also of therapeutic effects. Frequent ECG measurement is therefore recommended to monitor both cardiac disturbances due to digoxin toxicity and potential worsening of pre-existing cardiac disorders. Renal function should also be monitored, including serum urea and creatinine as well as estimated glomerular filtration rate. Monitoring of potassium, ECG and renal function should be continued until the patient has regained their pre-intoxication status, including achievement of 'normal' clinical status, resolution of ECG changes and potassium disturbances, and restoration of baseline renal function.

After toxicity has resolved, digoxin may need to be reinitiated or alternative therapy introduced. The timing of reinitiation and the dose given requires careful

consideration with sufficient time allowed for full clearance of digoxin immune Fab.

Adverse events associated with digoxin immune Fab treatment may occur up to 14 days after the administration of digoxin immune Fab [16,23]. Infusion-related and hypersensitivity reactions including serum sickness are possible but rarely occur.

Other treatment options
Cases of chronic digoxin toxicity with mild symptoms but without ECG changes or arrhythmias, or conduction disturbances, can generally be managed by stopping digoxin or reducing the digoxin dose. Patients should be carefully monitored for worsening of underlying heart failure or arrhythmia associated with reduced therapeutic action of digoxin.

Treatment with activated charcoal is not a substitute for other interventions, including use of digoxin immune Fab, but can be considered within the first 2 h following acute digoxin ingestion [24–26]. Caution is required in patients with confusion or a decreased consciousness level due to the risk of charcoal aspiration and consequent pneumonitis [27]. Extracorporeal treatments directed at enhancing the elimination of digoxin, such as dialysis and haemoperfusion, are of limited effectiveness [28] and are not generally recommended.

Severe hypokalaemia can be managed by intravenous administration of additional potassium. Potassium levels should be carefully monitored to avoid rebound hyperkalaemia. Mild-to-moderate hyperkalaemia should resolve following digoxin immune Fab treatment without the need for additional measures.

Alongside digoxin immune Fab as first-choice treatment, ventricular arrhythmias can be treated with lidocaine or magnesium sulfate, and bradyarrhythmias with atropine [29–32]. Adrenaline and isoprenaline can trigger ventricular fibrillation [33–35], and so should be avoided where possible. Cardiac pacing requires extreme caution [36] and, while necessary and beneficial for some patients [37], should only be undertaken if digoxin immune Fab is not immediately available and by clinicians with the requisite expertise and within a coronary care or cardiac intensive care setting.

Discussion
The consensus process produced a series of recommendations to help physicians to recognise and treat digoxin toxicity so as to improve outcomes for patients and enhance the efficiency of healthcare facilities in managing this challenging toxicity. One area of repeated discussion was the advice for dosing of digoxin immune Fab. The statements reflect the consensus that the presence or absence of cardiac arrest is the critical consideration. The pattern of toxicity (chronic, acute-on-chronic and acute) is less important in the emergency setting. The intention was to identify a simple and practical approach that can be rapidly implemented without the need for time-consuming calculations. Most patients with chronic toxicity have digoxin levels <5 ng/ml, and so 1–2 vials of digoxin immune Fab should usually be sufficient for full neutralisation [38–40]. The recommendation for an initial dose of five vials of digoxin immune Fab for patients in cardiac arrest is directed at balancing the clinical urgency of achieving neutralisation with the often limited supplies of digoxin Fab immediately available. Five vials (200 mg) of digoxin immune Fab will achieve neutralisation of 3 mg digoxin and is likely to be sufficient in most cases. However, other approaches to dosing have been recommended and used. The posology section in the labelling for DigiFab [15] is based on pharmacological considerations [41] and describes calculating the dose required to achieve half or full neutralisation of circulating digoxin, and taking into account the type of poisoning, body weight and whether the amount of digoxin ingested or the serum concentration of digoxin is known. Some authors have proposed initial dosing with half of the dose calculated as specified in the label, with further doses administered if required according to response [41].

A number of limitations should be noted. First, there is little robust evidence as to the effectiveness and safety of interventions for the management of digoxin toxicity. Therefore, the consensus process drew on personal experience and interpretation to a greater extent than is ideal. Second, all participants were based in Western Europe and, as such, the consensus is based on experience that may not be wholly representative of, or applicable to, management of digoxin toxicity in other parts of the world.

Conclusion
Digoxin toxicity presents a complex and challenging medical emergency that requires immediate management to achieve optimal outcomes. The consensus statements developed by a group of specialists in intensive care medicine, toxicology and cardiology provide practical and pragmatic recommendations for the management of digoxin toxicity in routine clinical care.

Acknowledgements

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