

Policy for the use of digoxin specific antibody (Digifab[®])

When using this document please ensure that the version you are using is the most up to date either by checking on the Trust intranet or if the review date has passed, please contact the author.

'Out of date policy documents must not be relied upon'

Approval Committee	Version	Issue Date	Review Date	Document Author(s)
Drugs and Therapeutics Committee	1	March 2013	March 2014	Jennifer Caverly Pharmacist, Dr Paul Andrews Acute Medicines Consultant

Version Control

Version	Date	Reviewed by	Section	Principle amendment Changes
2	November 2016	Michelle Windust Dorset CCG	Appendix 1 Page 9	Contact names and numbers updated.

Contents

Contents	Page No
1.0 Introduction	2
2.0 Objective / Policy Statement	3
3.0 Liability	3
4.0 Recognition of digoxin toxicity	3
5.0 Management of acute or acute-on-chronic digoxin toxicity	4
6.0 Use of DigiFab [®] in the treatment of digoxin toxicity	5
7.0 Obtaining supply of DigiFab [®]	7
8.0 Shared stock holding agreement	7
9.0 Procurement of DigiFab [®]	7
10.0 Audit	8
11.0 Implementation	8
12.0 Process for Monitoring Compliance with the Policy	8
13.0 References	8
14.0 Consultation	8
Appendix 1: Contact numbers for obtaining supply of DigiFab [®]	9
Appendix 2: Flowchart for management of digoxin toxicity	10
Equality Impact Assessment Form – Screening Form	11

1.0 Introduction

In a normal healthy heart, digoxin is rarely toxic unless the ingested dose is very high. Accidental overdose, e.g. in children or digoxin-naïve young adults, rarely requires treatment. Remember that symptoms of toxicity may be vague, especially in older patients. Markers of poor prognosis include hyperkalaemia, old age and underlying heart disease.

Digoxin toxicity is a serious medical condition that as previously mentioned can be difficult to recognise in patients whose health may already be compromised. Studies have shown that digoxin or digitalis poisoning can impact length of hospital stay.

DigiFab[®] Digoxin Immune Fab (Ovine) has an affinity for digoxin in the range of 10^9 to 10^{10} M⁻¹, which is greater than the affinity of digoxin for its sodium pump receptor, the presumed receptor for its therapeutic and toxic effects.

When administered to a patient, DigiFab[®] Digoxin Immune Fab (Ovine) binds to molecules of digoxin, reducing free digoxin levels, which results in a shift in the equilibrium away from binding to the receptors, thereby reducing cardiotoxic effects. Fab-digoxin complexes are then cleared by the kidney and reticuloendothelial system.

Digoxin - Pharmacokinetic parameters

Absorption	55 - 75% (for tablets)
Vd	5.6 L/kg
Protein binding	25%
t _{1/2}	34 hours
Excretion	Renal

2.0 Objectives

This policy describes this Trust's (which is shared with other Local Trust's) approach to the management of digoxin toxicity and to the use of DigiFab[®]. DigiFab[®] is an expensive product for which there is rarely a genuine clinical need and as such the decision has been made to share stock within the region. Small supplies will be held at The Royal Bournemouth Hospital, Poole Hospital, Dorset County Hospital and Salisbury District Hospital. Prescribing of DigiFab[®] thus presents the need to obtain the necessary stock from each of these locations in a timely manner so as not to put the patient at risk. The aim of this policy is to minimise risk and manage such patients effectively.

3.0 Liability

- The Trust will accept liability for the use of DigiFab[®] where it has been used in accordance with this policy. Where this policy has not been followed, responsibility will rest with the prescriber, pharmacist and nurse involved.
- When prescribing, all doctors must be satisfied that an alternative medicine or management strategy would not meet the patient's needs.
- Only a Consultant may authorise the use of DigiFab[®]. Junior medical staff may only prescribe DigiFab[®] with the permission of their Consultant.
- In the first instance, all requests (by telephone) should be forwarded immediately to the designated pharmacist (directorate or other senior pharmacist, or on-call pharmacist as appropriate) so that an adequate supply can be obtained.

4.1 Recognition of digoxin toxicity

4.2 Symptoms and signs of toxicity

These are often non-specific, and in patients on digoxin, a high index of suspicion is needed. They may include:

- Bradycardia, heart block (any type or degree)
- Ventricular dysrhythmias
- Hypotension
- Nausea and vomiting
- Abdominal pain / diarrhoea
- Visual disturbance - xanthopsia is uncommon
- Confusion

4.3 Important drug interactions that may have contributed

to Inhibited protein binding (increased free drug ratio)

- Clofibrate
- Warfarin
- Phenobarbital

Increased serum concentration

- Amiodarone
- Aspirin
- Diltiazem
- Flecainide
- Ibuprofen
- Propafenone
- Indometacin
- Spironolactone
- Clarithromycin (macrolides)

5.1 Management of acute or acute-on-chronic digoxin toxicity

5.2 Gastrointestinal decontamination

- In the conscious patient, within 1 hour, a single dose of activated charcoal (50g for an adult) can be given orally. There is no evidence that use after 1 hour of ingestion, multi-dose charcoal, or use of single-dose charcoal in chronic overdose, is of any clinical value

5.3 Extracorporeal elimination

- There is no evidence to suggest that extracorporeal elimination techniques (haemoperfusion, haemodialysis, ultrafiltration or MARS dialysis) confers clinical advantage.

5.4 Correction of electrolyte imbalances

- **Hypokalaemia:** Care is needed with correction of hypokalaemia as injudicious use of potassium replacement may lead to rebound hyperkalaemia.
- **Hyperkalaemia** should not be treated with calcium gluconate / calcium chloride unless there is no prospect of obtaining Digifab[®], and the hyperkalaemia is life-threatening. Intracellular calcium concentrations are already high, and ***additional calcium will dramatically increase the risk of ventricular arrhythmias.*** Digifab[®] will correct hyperkalaemia and in the setting of severe toxicity is the preferred therapeutic strategy.
- **Hypocalcaemia:** Asymptomatic hypocalcaemia should not be treated routinely.

5.5 Treatment of brady/tachyarrhythmias

- **Magnesium** – this can be used even if the potassium level is high. It potentiates Na/K/ATP-ase activity but does not influence protein binding.
- **Cardiac pacing** – this can be problematic and is best avoided in acute toxicity. The potential for malignant rhythm disturbances, coupled with the need in the poisoned patient for extremely high pacing potentials to achieve mechanical capture, render it far less satisfactory than antidote treatment with Digifab[®].

- **DC-cardioversion:** this is best avoided. Even at the lowest energy settings on modern biphasic defibrillators, the highest mortality rates for DCCV occur in the setting of digoxin toxicity.

6.1 Use of DigiFab[®] in the treatment of digoxin toxicity

6.2 Primary indications:

- Asystole
- VF / VT
- Profound bradycardia – pulse < 40 beats per minute despite adequate atropinisation (e.g. 3mg in total)
- Hyperkalaemia – serum potassium \geq 5.5mmol/L

6.3 Secondary indications- consider use if symptomatic intoxication and any of the following:

- Age > 65 years
- Pre-existing structural cardiac disease
- Bradycardia – pulse < 60 beats per minute despite atropine
- Second / third degree SA / AV block
- Serum potassium > 5mmol/L

6.4 Dosage

Number of 40mg vials to use can be calculated by:

1. Ingested dose in **milligrams** x 1.6 (round to nearest vial then prescribe dose in mg by multiplying number of vials by 40) Please note digoxin tablets are available in 62.5, 125 and 250**micrograms**

For example: if 56 x 62.5microgram tablets are ingested
 = $56 \times 0.0625 \times 1.6 = 5.6$ **vials** → round to nearest vial (6 vials)
 prescribe as 240mg (6 x 40mg)

2. **OR** Serum concentration in nanograms/ml or micrograms per litre x weight in kg x 0.01
3. For children < 20kg when the serum concentration of digoxin is not known; 1 vial of DigiFab should be adequate for full neutralisation.

NB: in practice, the amount required is almost always 8 to 10 vials. More than 1:1 neutralisation using digoxin-specific antibodies is of no clinical consequence.

A sensible guide is to give 8 - 10 vials in acute toxicity, and 6 - 8 in chronic accumulation.

- **Beware of using reported serum levels in determining dose of DigiFab[®], as commercial assays become unreliable at serum digoxin concentrations greater than 6.4ng/ml.**

6.5 Administration

- Dissolve **each vial** in 4ml of sterile water for injections.
- Dilute the total amount to be infused with 0.9% (normal) saline as required – 250-500ml is usually sufficient for the entire dose to be administered (approx. 50ml per vial). The full dose will probably need to be given in separate stages due to expected delays in obtaining the medicine. Diluent volume should be adjusted accordingly (see section 7.2). Give intravenously over a total of about 1 hour.

Please note: Due to our shared stock holding it is unlikely that treatment will be given as one single infusion

6.6 General management of patients

Dosage estimates are based on a steady-state volume of distribution of 5L/kg for digoxin in order to convert serum digitalis concentration to the amount of digitalis in the body. These volumes are population averages and vary widely among individuals.

Usually, improvements in the signs and symptoms of digoxin toxicity begin within 30minutes following administration of DigiFab[®].

Patients should have continuous electrocardiographic monitoring during and for at least 24 hours after administration of DigiFab[®]. Temperature, blood pressure and potassium concentrations should also be monitored closely.

Patients previously dependent on the inotropism of digoxin may develop signs of heart failure when treated with DigiFab[®]. After successful management of poisoning, digoxin has had to be reinstated in some cases.

If, after several hours, toxicity has not adequately reversed or appears to recur, re-administration of DigiFab[®] at a dose guided by clinical judgement may be required.

Failure to respond to DigiFab[®] should alert the physician to the possibility that the clinical problem may not be due to digoxin toxicity.

If an anaphylactic reaction occurs during an infusion then administration of DigiFab[®] should be stopped immediately. The likelihood of this occurring may be higher in patients that are allergic to sheep-derived products or papain (an extract of the papaya fruit). There is also an increased of anaphylaxis with repeated dosing.

In patients with renal impairment the rate of excretion of the DigiFab-digoxin complexes is slowed and as such digoxin may be released after some days from retained complexes.

Common adverse reactions to be aware of include hypokalaemia, hyperkalaemia, headache, confusion, nausea, vomiting, diarrhoea, constipation, abdominal distension, worsening of cardiac failure, chest pain, hypotension, orthostatic hypotension, influenza-like illness, renal failure, fatigue and infusion site phlebitis.

If there are any uncertainties regarding a patient the national poisons helpline should be contacted **(NPIS 0844 892 0111)**.

7.1 Obtaining a supply of DigiFab®

7.2 Contacting pharmacy

When assessed by the consultant that DigiFab® is required according to this guideline and appendix 2 (flowchart) the first step is to notify the designated pharmacist (ward pharmacist/senior pharmacist/on-call pharmacist) as appropriate in the situation.

7.3 Initiating treatment

Treatment should be initiated with local trust supply of DigiFab® available in emergency drug cupboard. There will be 3 vials kept on site in total. These 3 vials can be diluted with about 100-150ml normal saline or any convenient volume and given over 20mins to commence treatment.

Treatment can then only be continued when supplies from other trusts arrive and the infusion can be restarted in the same manner at each arrival of DigiFab® until the required number of vials has been administered. Interruptions in infusions due to transport of DigiFab® from other locations (especially out of hours) must be accounted for in prescribing e.g. 3 - 4 separate infusions depending on required dose.

7.4 Role of the pharmacist in obtaining supply of DigiFab

It is the responsibility of the designated pharmacist when contacted by the clinicians to initiate the chain of supply. The pharmacist should contact the pharmacy departments / on-call pharmacists via the contact numbers listed in appendix 2 immediately after confirming there is a legitimate need for DigiFab®. The nearest Trust should be contacted first and so on to ensure the patient gets a sufficient dose in the first hour or two of treatment.

Transport should be arranged to transfer DigiFab® between trusts (with assistance from clinical site). The taxi should be instructed to take the DigiFab® straight to the appropriate ward.

7.5 Ensuring safety of supply

If there is a pharmacist present on the ward when the supply arrives the product should be checked by the pharmacist prior to administration. In the absence of a pharmacist it is the responsibility of the medical staff to check the product is correct and suitable for use (e.g. it hasn't expired). The nurse should repeat this checking process prior to administration.

8 Shared stock holding agreement

This policy is dependent on the understanding that all four hospitals in the region will keep a supply of no less than 3 vials of DigiFab® and be willing to share supplies if or when they are required by another Trust. If at any time a trust within this agreement fails to supply or the combined supply is insufficient to meet the clinical need of the patient supplies should be sought from Southampton General Hospital.

9 Procurement of DigiFab®

Pharmacy procurement must ensure that between RBH and PGH a total of 6 vials of DigiFab® are stocked.

10 Audit

The storage of DigiFab[®] will be reviewed annually by pharmacy and if necessary the Drug & Therapeutics Committee. This should include a review of any newly licensed and/or less expensive products introduced to the market which would negate the need to share stock across the region.

Any DigiFab[®] related AIRS forms submitted by prescribers or pharmacists should be brought to the attention of the D&TC.

11 Implementation

All DigiFab[®] prescribing must comply with the policy. RBH and PGH will purchase DigiFab[®] with the understanding that it will only be used appropriately as outlined in this guideline and in appendix 2.

12 Process for monitoring compliance with the policy

Pharmacy will monitor compliance with the policy, for example; appropriateness of out of hours DigiFab[®] prescribing will be assessed retrospectively by the ward pharmacist and discussed with the prescribing team.

13 References

- DigiFab[®] 40mg/vial Digoxin immune Fab powder for solution for infusion. MHRA SPC, available online at:
<http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con126289.pdf>
- Guidelines and advice from Dr Paul Andrews BM, MRCP (UK), MRCP (London), P G Dip Med Tox, Acute Medicine, Emergency Medical Unit, Dorset County Hospitals NHS Foundation Trust (see appendix 2 Flowchart)
- www.toxbase.org accessed 14/2/13

14 Consultation

<p>Those listed opposite have been consulted and comments/actions incorporated as required.</p> <p>(Author to ensure that relevant individuals/groups have been involved in consultation as required prior to this document being submitted for approval)</p>	<p>Paul Andrews, Acute medicine consultant DCH Alison Fitzpatrick, Cardiac pharmacist RBCH Ellen Sinden, PGH pharmacist Deirdre Terrot, Paediatric and Nutrition pharmacist, PGH Carl Partridge, PGH Chief Pharmacist Martin Shepherd, DCH pharmacist Peter Davies, Salisbury pharmacist A&E and cardiac consultants, RBCH</p>
--	--

Appendix 1:

Contact numbers for obtaining supply of DigiFab®

Royal Bournemouth and Christchurch Hospitals:

- Nettie Aubry 01202 704103
- Alternatively any available senior pharmacist 01202 704099
- Out of hours: On-call pharmacist via switchboard 01202 303626

Poole Hospital:

- Dispensary: 01202 263377 Ask for the Pharmacist on Duty
- Out of hours: On-call pharmacist via switchboard: 01202 665511

Salisbury District Hospital Salisbury:

- Suzanne Bennett: 01772 336262 Ext: 4277
- Out of hours: On-call pharmacist via switchboard: 01722 336262

Dorset County Hospital Dorchester:

- Martin Shepherd: 01305 255171
- Out of hours: On-call pharmacist via switchboard: 01305 251150

Southampton General Hospital:

- On-call pharmacist via switchboard: 023 8077 7222

Other helpful contact numbers:

[National poisons helpline](#) (NPIS) UK 0344 892 0111

Blood Runners

Free, out of hour's, emergency (blue-lighted) transport of medicines within Dorset

www.servwessex.org.uk

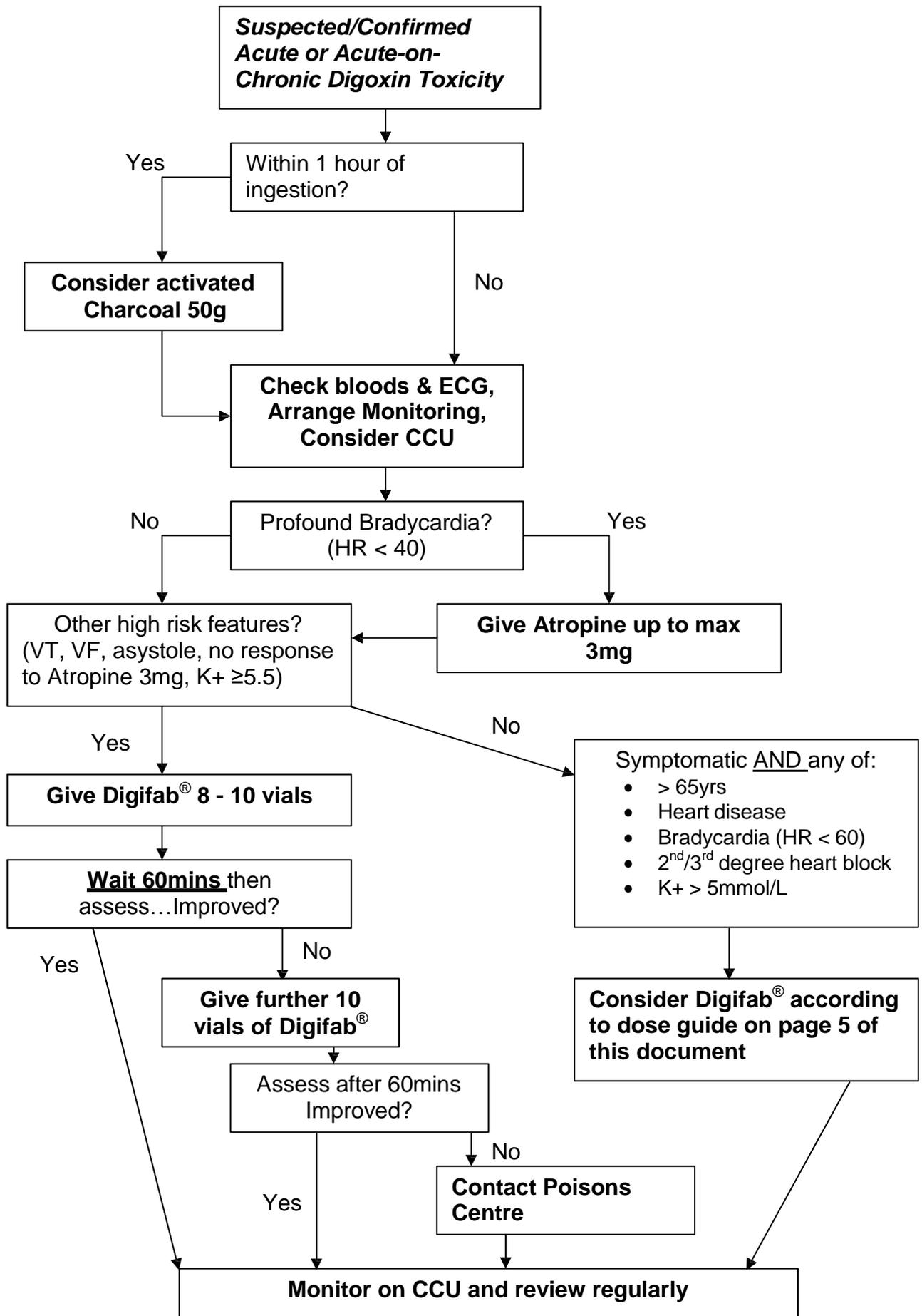
07017891008 / 07017890999

Operates: 365 days of the year

Monday to Friday: 19:00 to 06:00

Weekends and Bank Holidays: 24 hour cover

Appendix 2: Guideline for the management of Digoxin Toxicity



EQUALITY IMPACT ASSESSMENT – SCREENING FORM

1. Title of document/service for assessment	Policy for the use of digoxin specific antibody (Digifab®)
2. Date of assessment	March 2013
3. Date for review	March 2015
4. Directorate/Service	Trust-wide
5. Approval Committee	D&TC

	Yes/No	Rationale
6. Does the document/service affect one group less or more favourably than another on the basis of:		
• Race	No	
• Gender (including transgender)	No	
• Religion or belief	No	
• Sexual orientation, to include heterosexual, lesbian, gay and bisexual people	No	
• Age	No	
• Disability – learning disabilities, physical disabilities, sensory impairment and mental health issues	No	
• Marriage and Civil Partnership	No	
• Pregnancy and Maternity	No	
7. Does this document affect an individual's human rights?	No	
8. If you have identified potential discrimination, are the exceptions valid, legal and/or justified?	N/A	

9. If the answers to any of the above questions is 'yes' then:	Tick	Rationale
Demonstrate that such a disadvantage or advantage can be justified or is valid		
Adjust the policy to remove disadvantage identified or better promote equality		
If neither of the above possible, submit to Diversity Committee for review.		

10. Screener(s)

Print name: Jacqui Bowden

11. Date Policy approved by Committee	7 March 2013
--	--------------

12. Upon completion of the screening and approval by Committee, this document should be uploaded to papertrail.