

**Chronic heart failure: management of chronic heart failure in
adults in primary and secondary care**
A clinical guideline for the NHS in England and Wales

APPENDIX J: EVIDENCE TABLES

Section 8: Monitoring

Digoxin monitoring

Experimental Studies

Paper	Reid, L. D., Horn, J. R., & McKenna, D. A. 1990, "Therapeutic drug monitoring reduces toxic drug reactions: a meta-analysis", <i>Therapeutic Drug Monitoring</i> , vol. 12, no. 1, pp. 72-78.
Description	Systematic review
N=	n=17 studies (7 of digoxin) n~6239 patients Patient characteristics Not stated USA reviewers of international studies
Intervention	Therapeutic drug monitoring programmes of either reporting serum concentrations to the attending physician, or in addition a recommendation on dosage adjustment, or a service which is responsible for the timing of the serum assay and dosage adjustment, versus conventional treatment
Outcomes	The outcome common across all studies was frequency of toxic drug reactions, however the criteria for determining this outcome was not explicitly stated in 8 of the 17 studies, and where it was stated the criteria varied.
Results	<ul style="list-style-type: none"> • Monitoring by TDM appeared to reduce the number of toxic reactions in 16 of the 17 papers included • The Mantel-Haenzel summary odds ratio for the combined studies gives a risk of experiencing a toxic reaction when TDM used as OR 0.35 (95% CI 0.13 – 0.89) (p=0.001). • It would take a further 6 studies with no effect to reduce the overall effect size to 0.2. • There was very little change when the before and after or cohort trials were analysed separately. • The overall effect size was 0.26 from all 17 studies, but when the 7 digoxin studies were analysed separately this was more marked at 0.33 (a small to moderate effect size)
Comments	<p>Not all HF population</p> <p>24 papers were identified - 2 were excluded because of incomplete data and 8 excluded because they lacked a comparison group</p> <p>Too few studies were available to determine whether confounding factors of concomitant medication, or co-morbidities modify the relationship between TDM and toxic reactions</p> <p>The cost-benefit of TDM services remains equivocal.</p> <p>It is likely that the results of this study are relevant to the guideline target population or at least those receiving digoxin</p> <p>A range of drugs considered in primary studies</p> <p>A search of Medline and Medlars, and other databases from 1966 to 1986 with conference proceedings and abstract journals with hand searching of reference lists.</p> <p>A subgroup analysis of different drugs is made, and no statistical heterogeneity between all the studies was recorded (Chi squared =14.04, df =16, p>0.05)</p>

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Studies included	Horn (1985), Kimblatt (1986), Coodley (1983), Mungall (1983), Sveska (1985), Kock0Weser (1974), Jelliffe (1972), Lewis (1976), Duhume (1974), Lehmann (1982), Whiting (1984), Cahil (1986), Bootman (1979), St Vincent Health Center Antibiotic Usage Review Sub-committee (1985)

Paper	Dasgupta, A., Saldana, S., & Heimann, P. 1990, "Monitoring free digoxin instead of total digoxin in patients with congestive heart failure and high concentrations of digoxin-like immunoreactive substances", <i>Clinical Chemistry</i> , vol. 36, no. 12, pp. 2121-2123.
Description	Cohort study
N=	n=34, congestive HF=12, no pathological condition to increase DLIS =22 Demographic and clinical characteristics of included patients not stated. USA
Intervention	HF patients displaying signs of congestion that may increase DLIS in blood serum are compared to patients without these
Outcomes	The final outcome assessed is the ration of free to total digoxin in blood serum
Results	<ul style="list-style-type: none"> • Concentrations of DLIS were considerably higher in HF patients (0.45 nmol/L) compared to healthy individuals (0.28 mmol/L) (p=0.0052) •The mean ratio of free to total digoxin in patients with HF on digoxin was 58.2% which was statistically lower than the ratio in patients on digoxin with no pathological condition that would increase DLIS 72.7% (p<0.05)
Comments	<p>Not measuring outcome of monitoring.</p> <p>DLIS interference in the sera of patients with congestive HF is significant considering the narrow therapeutic range of digoxin.</p> <p>Concentrations of albumin were not significantly different between the two groups</p> <p>Free digoxin is the pharmacologically active fraction, and correction for DLIS interference should be considered in patients with congestive H</p> <p>Potentially confounding factors in patient characteristics between the two arms</p> <p>Low numbers in HF population arms</p> <p>A good replicability of assay for digoxin levels, with within run and between run variability assessed, and temperature control of laboratory evaluated to be sufficiently constant</p>

Non-experimental studies

Paper	Canas, F., Tanasijevic, M. J., Ma'luf, N., & Bates, D. W. 1999, "Evaluating the appropriateness of digoxin level monitoring", <i>Archives of Internal Medicine</i> , vol. 14, no. 1, pp. 363-368.
Description	Audit
N=	
Intervention	
Outcomes	
Results	<ul style="list-style-type: none"> • Of 224 digoxin measurements from inpatients (55% male, mean age 68 years) only 16% (95% CI 11- 20%) were classified as an appropriate indication. Of the 84% that had no appropriate indication 76% were due to early routine monitoring, and 9.5% were done on patients not receiving digoxin. • The results of the inappropriate tests indicated 31% of the patients on a sub therapeutic dose (<1.2nmol/L) and 14% of patients with a potentially toxic drug level (>2.3nmol/L) although none of these resulted in a change of therapy regimen • Of 130 digoxin measurements from outpatients (50% male and mean age of 68 years) 52% (95% CI 44 - 61%) had an appropriate indication to do so. Of the 48% of measurements that were taken inappropriately 76% were due to early routine monitoring. • As appropriateness of request for serum digoxin measurement depended on clinical indication being for AF or congestive HF these populations were analysed separately, however the results were similar. • The results of the inappropriate tests in outpatients showed 6% with a drug level of >2,3nmol/L, of these 4 patients 1 received a decreased dose of digoxin, while in the others no therapeutic change was noted. • Overall inappropriate measurements were made at a rate of 80% • Levels should be performed to answer a particular clinical question or to monitor a stable patient's condition at reasonable time points. • There are few data available regarding the frequency of monitoring stable, asymptomatic outpatients, and the timing of dose change monitoring is open to changes in half-life between patients. • Study only used certain laboratory parameters as markers for patients function • Propriety may not be generalised to other organisational settings • Chart review may not always reveal the reasons for ordering a digoxin level. Patient symptoms and suspected non-compliance may not have been recorded.

<p>Comments</p>	<p>A study with various goals including to evaluate the proportion of digoxin determinations with an appropriate indication, and to determine how often inappropriate assessments generated clinically important results Retrospective case audit from a tertiary care university hospital Criteria for and appropriate investigation derived from a Medline literature search, and cross reference and review, followed by a revision by an expert panel including cardiologists, and internist, and a clinical pathologist. A six point appropriate serum digoxin level request protocol was developed with indications including: Subtherapeutic response Suspected toxicity High risk patient Initiation of digoxin or change of dose Admission level of digoxin if none available in last 9 months for inpatients Annual monitoring for outpatients on stable dose of digoxin Case notes were retrieved on basis of random number generation to include 5% of inpatient and 12% of outpatients during a 6 month period Various demographic, clinical, and process of care elements were retrieved from case notes and computerised records and used to assess each request for serum digoxin measurement as appropriate or inappropriate. A random sample of cases included were reassessed blind by an independent reviewer, showing an inter-rater agreement of K=0.65. Not looking out outcomes of improved monitoring.</p>
<p>Reference</p>	<p>213</p>

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Paper	Howanitz, P. J. & Steindel, S. J. 1993, "Digoxin therapeutic drug monitoring practices: A College of American Pathologists Q-probes study of 666 institutions and 18 679 toxic levels", <i>Archives of Pathology & Laboratory Medicine</i> , vol. 117, no. 7, pp. 684-690.
Description	Audit
N=	
Intervention	
Outcomes	
Results	<ul style="list-style-type: none"> • n=280 172 specimens • USA, Canada, Australia. • Both AF and HF patients of all ages • 6.7% of the specimens audited provided results of greater than 2.6 nmol/L, which was used as the upper limit for therapeutic range in 74% of the institutions participating • Of all the elevated digoxin samples 67% of these were taken at least 8 hours after the last dose, 9% were taken between 6 and 8 hours after last dose, and 24% were taken within 6 hours of the last dose. • Only 10 institutions required the time of the last digoxin dose to be included on requisitions and would not perform the analysis if this was not received • Of the elevated digoxin samples 77% followed oral doses, 23% intravenous doses, and less than 1% following intramuscular. • Physician often assume that the laboratory is using the correct therapeutic range, and that samples are taken at the appropriate time. • There is an overlap between toxic and therapeutic digoxin ranges as toxicity is influenced by potassium calcium and magnesium levels, and by renal failure or hypoxia. • Delays in phlebotomy or patient unavailability in the early morning may result in sampling after drug ingestion. • Approximately 25% of all specimens were taken at inappropriate times, less than 6 hours after the last digoxin dose.
Comments	<p>Part of a quality improvement programme of the American College of Clinical Pathologists, aimed to improve patient care by standardising digoxin monitoring procedures</p> <p>666 institutions provided information on 280 172 serum specimens and process of monitoring</p> <p>Data was collected data for 3 months or until 50 consecutive occurrences of elevated digoxin concentrations were found.</p> <p>Elevated digoxin was defined as being >2.6 nmol/L</p> <p>For each specimen the time drawn was noted, as was the route and time of the last dose. Timings of investigation were grouped as being less than 6 hours, between 6 and 8 hours, or more than 8 hours after last dose.</p> <p>Details of management practices within institutions were detailed in terms of pharmacokinetic services being either formal or informal, being provided by either laboratory or pharmacy, or was another type, and what policy the laboratory used for recording the digoxin dose times on requisitions</p>
Reference	212

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Paper	Matzuk, M. M., Shlomchik, M., & Shaw, L. M. 1991, "Making digoxin therapeutic drug monitoring more effective", <i>Therapeutic Drug Monitoring</i> , vol. 13, no. 3, pp. 215-219.
Description	Before and after study
N=	
Intervention	
Outcomes	
Results	<ul style="list-style-type: none"> • n=6 • USA • In 6 randomly selected inpatients before the policy change 13 out of 50 (26%) of the serum digoxin concentrations were inappropriately checked less than 12 hours after last dose. After the policy change a sample of 3 inpatients demonstrated only 3 out of 51 (5.9%) inappropriately timed digoxin levels • Inappropriate data is both costly and can adversely influence the decision making of the attending physician. • After a change in dosage, digoxin concentrations should not be checked for at least several days (unless there are signs or symptoms of toxicity) as apparent fluctuation between subtherapeutic and toxic concentrations may be falsely recorded. • Daily measurement for patients who are known to be clinically stable should be avoided.
Comments	<p>An evaluation of a programme of dosing and monitoring policy to reduce the number of serum samples drawn too soon and to improve digoxin therapeutic drug monitoring (TDM)</p> <p>A before and after study using a randomly selected patients cohort (method of randomisation not stated)</p> <p>Digoxin concentrations measured by an immunoassay.</p> <p>Time period for effective measurement of digoxin concentration set at >12h after last dose, and where a change in dose evaluation should be made after 5 half lives of the drug have elapsed</p> <p>The programme stipulated that all digoxin dosing were regimented to 17:00 and serum drawn for analysis at 07:00 the next day.</p> <p>Information on cases from retrospective chart review</p>

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Paper	Tuncok, Y., Hazan, E., Oto, O., Guven, H., Catalyurek, H., & Kalkan, S. 1997, "Relationship between high serum digoxin levels and toxicity", <i>International Journal of Clinical Pharmacology & Therapeutics</i> , vol. 35, no. 9, pp. 366-368.
Description	Case series
N=	
Intervention	
Outcomes	
Results	<ul style="list-style-type: none"> • n=1269 patients • Turkey • Thoracic and cardiovascular surgical ward. • Only 4.6% of patients found to have a high serum digoxin (over 3.0ng/ml) • Of 58 patients with high digoxin levels only 11 (22.9%) of them showed toxicity • Neither Age nor sex were factors for the development of clinical digoxin toxicity • Serum potassium levels were found to be higher in patients without as opposed to with toxicity 4.6mmol/l Vs 4.3 mmol/l (p=0.01) • All patients classified as having toxicity manifested in nausea and vomiting, with premature ventricular contractions present in 2 patients and atrial fibrillation in another • Overall 8.7% of all patients and 22.9% of patients with elevated serum digoxin levels had clinical toxicity
Comments	<p>A retrospective study of cases to determine the relation ship between serum digoxin levels of 3.0 ng/ml or higher and clinical toxicity Only patients undergoing surgery included, where digoxin concentrations were drawn and analysed using a fluorescence polarisation immunoassay with 95% sensitivity.</p> <p>Toxicity defined as having gastrointestinal or central nervous signs or symptoms, or ECG evidence of dysrhythmia.</p> <p>Patients with and without toxicity were matched for demographic characteristics and for several serum biochemical concentrations</p> <p>Data could be biased to showing lower toxicity with high serum levels as the drug was discontinued immediately after high serum digoxin level was obtained</p>

Paper	Valdes, R. Jr., Jortani, S. A., & Gheorghiade, M. 1998, "Standards of laboratory practice: Cardiac drug monitoring", <i>Clinical Chemistry</i> , vol. 44, no. 5, pp. 1096-1109.
Description	Guidelines
N=	
Intervention	
Outcomes	
Results	<ul style="list-style-type: none"> • Commercially available automated immunoassays are available for digoxin in clinical laboratories • Common side effects of digoxin include Nausea Vomiting Visual disturbances Weakness • Major toxic effects include AV block Premature cardiac contraction Arrhythmia Vomiting • Other monitoring requirements include Potassium concentrations and ECG • Time to steady state after digoxin 5 to 7 days with a half life of 26 to 52 hours a therapeutic range is deemed to be at 0.0005 to 0.002 mg/L and toxic concentrations are found in excess of 0.003 mg/L. • Digoxin overdose can cause hyperkalaemia from reduced activity of sodium pump, therefore in suspected cases whole blood or serum potassium should be measured • Sampling time should be 8 to 12 hours or more after last dose. Serum or plasma sample should be taken (SST tubes should not be used). The sample will remain stable for 24hrs at 2 to 8 °C, or for 1 to 2 weeks at -20 °C. Immunoassays with active metabolites cross-reacting in proportion to their biological activities are desired • Other situations where serum monitoring is recommended include digitalis intoxication, in patients with decreased renal function to adjust digoxin dosage, or where other drugs known to interact with digoxin are co-administered • Measuring the unbound digoxin levels may be possible by using ultrafiltration before the immunoassay, or by the development of immunoassays that will directly measure only the unbound fraction of digoxin. • Digoxin should not be measured on samples from patients who have received an antidotal therapy, or the laboratory must demonstrate that the method used is not adversely affected by this.

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Comments	No details of methods utilised to develop the guidelines n=118 references Guideline covers all cardiac drugs each in terms of pharmacokinetic information, collection logistics, analytical issues, and indications for monitoring Aim to recommend guidelines for therapeutic monitoring of cardiac drugs, but no explicit outcomes are defined
Reference	211