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# An up-to-date review of digoxin toxicity and its management

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**Abstract**
The main focus of this review article was to discuss digoxin, causes of digoxin toxicity, management of digoxin toxicity in patients, and how it can be treated. Digoxin belongs to a category of drugs known as cardiac glycosides. Digoxin comes from foxglove leaves. Though discovered in 1785, digoxin had been in use for more than 2000 years ago. Patients suffering from heart failure and taking digoxin need to take diuretics to dehydrate excess water from their bodies. Diuretics enhance potassium loss, and resultant potassium levels increase the risk of digitalis toxicity. Patients ought to be continuously monitored by clinicians for any signs or symptoms of digoxin toxicity as they use the available preventive measures. Some of these measures are: assessing electrolytes, measuring digoxin serum concentrations, evaluating pharmacotherapy treatments for any possible drug interactions, and determining digoxin treatment basing it on pharmacokinetic parameters. In the event of digoxin toxicity occurrence, the clinical condition of the patient should be assessed in order to implement treatment. If appropriate care is taken, digoxin treatment can be safe, effective, and cost-effective. Finally, digoxin toxicity can be treated using activated charcoal, which lowers toxicity levels in patients from 30% to 40% within 12-18 hours. Specific digoxin antibody-fragments (digoxin immune Fab) can be used in the treatment of life-threatening digoxin toxicity. The fragments available in the market are DigiFab and DigiBind, which originate from ovine, gathered and cleaned from sheep, immunized with human albumin and combined with digoxin. These digoxin molecules combine with antibody-fragments to prevent them from combining with their receptors.

**Keywords:** digoxin, heart failure, cardiac glycoside, bioavailability, $Na^+/K^+$-ATPase pump, vagal activity, digoxin toxicity, digoxin immune Fab, digoxin management

## 1. Introduction
Digoxin is a drug substance belonging to a category of medications referred to as cardiac glycosides. Cardiac glycosides contain a five or a six-membered lactone ring attached to the steroid nucleus at position 17. For almost more than 300 known digitalis compounds, two natural products have been used frequently in clinics: digoxin and ouabain. Ouabain is derived from *Strophanthus gratus* plant, while digoxin comes from foxglove leaves (*Digitalis purpurea*) [1, 2]. Though the medical efficiency of a *Digitalis purpurea* was discovered in 1785 by English medical doctor William Withering, both digoxin and Ouabain have been in use for medicinal purposes for more than 2000 years [3, 4]. Being both a medical doctor and a botanist, Dr. Withering was aware of the remedies for a disease referred to dropsy (excessive fluid retention). He also believed that digitalis produced a diuretic effect in those with an irregular, weak pulse, and concomitant edema [3, 5].

## 2. Pharmacology of Digoxin
Digoxin is composed of a sugar (glycone) and a cardenolide (aglycone) moieties; its molecular formula is $C_{41}H_{64}O_{14}$, and its molecular weight is 780.95 Da (Figure 1) [2]. Digoxin is sold under the brand name Lanoxin and is considered one of the top poisons in the world due to: i) Wide availability, and, ii) Narrow therapeutic window [2].

### Pharmacokinetics of Digoxin
The bioavailability of digoxin varies depending on the dose. In tablets form, the bioavailability ranges from 60% to 80%; a value of 70% is often used as the standard. Whilst soft-gelatin digoxin capsules appear to get completely absorbed (bioavailability=100%) and digoxin elixir exhibits a bioavailability of approximately 80% [6]. When digoxin is given intravenously, it is known to have a bioavailability of 100%. Medications such as clarithromycin, erythromycin, and itraconazole can raise the bioavailability of digoxin while products like charcoal, cholestyramine, and St. John's wort can reduce the bioavailability of digoxin. Based on the ideal body weight, the average volume of digoxin distribution is about 7.3 l/kg [6]. Therefore, digoxin is distributed widely throughout the body. Though digoxin is water-insoluble, $Na^+/K^+$-ATPase pumps are located in all tissues and digoxin binds to these pumps, accounting for its wide distribution throughout the body's tissues [7]. This feature is essential in the treatment of digoxin toxicity with digoxin immune Fab as the drug distributed in the tissue compartments will re-equilibrate following initial antibody fragment treatment. Equations are also available for more patient-specific calculations of digoxin's volume of distribution that consider patient weight and creatinine clearance. Besides, some other factors may change its volume of distribution; quinidine and hypothyroidism reduce volume, whereas hyperthyroidism increases volume [6]. Digoxin distributes relatively slowly following a two-compartment model, and complete distribution typically takes approximately 3-4 hours. Since the heart responds as part of the second compartment, therapeutic effects are delayed until the distribution is complete. The clearance of digoxin involves both metabolic and renal clearance from

the body. Approximately 10-30% of the population, metabolic elimination partially takes place as a result of the conversion of digoxin to digoxin-reduction products by *Eubacterium lentum* in the gut [8]. Another component of digoxin metabolism is postulated to occur because of hepatic conversion to 3-keto-digoxigenin and 3-epidigoxigenin metabolites, followed by conjugation [9]. Moreover, digoxin is metabolized in the stomach by gastric acid, which removes digitoxose sugars to form deglycosylated congeners. These sugars are hydrolyzed, and the resulting products are oxidized and undergo epimerization through hepatic uridine diphosphoglucose-glucuronosyltransferase, followed by conjugation [10, 11]. Overall, the metabolic clearance of digoxin averages approximately 0.8 ml/kg/min. The renal clearance of digoxin is generally equivalent to creatinine clearance. In patients with heart failure, both the metabolic and renal components of digoxin clearance decrease; however, the metabolic component decreases more dramatically. The clearance of digoxin is also reduced in patients with hypothyroidism and in drug interactions with amiodarone, quinidine, and verapamil. Alternatively, clinical hyperthyroidism may increase digoxin clearance [6]. In patients with normal renal function, the $t_{1/2}$ of digoxin ranges 36-48 hours. In those with renal insufficiency, the $t_{1/2}$ can increase to 6 days [6, 9]. This has obvious implications for the timing of serum sampling for measurement of serum digoxin levels as discussed further in the following section.

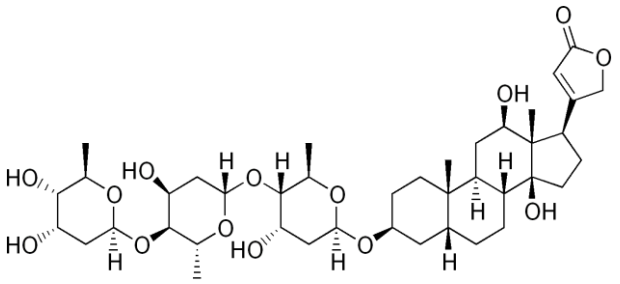


**Fig 1:** Chemical structure of digoxin [2].

## 3. Measurement of Digoxin Serum Concentrations

Since there are similarities between the therapeutic and toxic digoxin serum levels, the symptoms and signs of digoxin toxicity may be reported in patients whose levels are within the therapeutic threshold, while others may have no symptoms when their digoxin serum levels are above the therapeutic range [9]. The therapeutic level for digoxin might be low for those suffering from heart failure as compared to the traditionally accepted level (0.5-2 ng/ml) [12, 13, 6, 9].

However, digoxin's effects on rate control in atrial fibrillation may require levels on the higher end of that range [9]. Thus, the measurement of digoxin serum concentrations is necessary when monitoring this medication to ensure its safe and effective use. As is true in therapy with any drug whose dosage is based on serum drug concentrations, the routine measurement of digoxin levels should occur once the steady state has been reached. Since the steady state is assumed following 3-5 half-lives of a consistent dosing regimen, using five half-lives should ensure a steady state for a drug such as digoxin, which can demonstrate variations in pharmacokinetic values, based on distribution and clearance. Notably, in a patient with a normal renal function who receives digoxin therapy, the steady state should be achieved after at least 7-10 days of treatment. In patients experiencing end-stage renal disease (ESRD), the lengthened $t_{1/2}$ of digoxin means the steady state will be achieved in 15-20 days. Digoxin levels should be measured once the steady state has occurred, but the distribution of a given dose must also be taken into consideration. Due to the relatively long distribution phase of digoxin, drawing levels within this phase can be best avoided by drawing trough levels. However, if one must draw a level sooner for practical concerns related to timing, waiting at least 4 hours after an intravenous dose or 6 hours after an oral dose is generally sufficient [6]. Some recommended indications for the cost-effective use of serum digoxin monitoring include: i) following initial digoxin doses, ii) to ascertain patient adherence with therapy, iii) in patients with dynamic or impaired renal function, iv) in patients receiving potentially interacting concomitant medications, v) in patients not experiencing adequate clinical response, and, vi) to prevent and diagnose toxicity [14]. Some individuals such as neonates, pregnant women, patients with renal failure, and those with hepatic failure, who are not taking digoxin possess digoxin-like immunoreactive substances that can interfere with the measurement of digoxin levels via immunoassay [15, 16]. Awareness of this possibility ensures that clinicians heed such factors when interpreting serum digoxin concentrations. A patient's clinical condition should always be considered in conjunction with measured serum concentrations when adjusting digoxin-dosing regimens, so that serum concentrations are not the sole indicator used in the decision-making process.

## 4. Mechanisms of Action and Clinical Indications of Digoxin

The therapeutic indications of digoxin are based on its mechanisms of action, which include effects on cardiac rate and rhythm, and the force of cardiac contraction (Figure 2). The slowing of cardiac rate and rhythm are attributed to digoxin's impact on the central nervous system (CNS) that leads to increased vagal activity resulting in slowed conduction in the atrioventricular (AV) node. The increase in the force of cardiac contraction is attributed to digoxin's binding to the $Na^+/K^+$-ATPase pump. By binding to the $K^+$-binding site of the pump, digoxin leads to inhibition of the pump. The consequent rise in $Na^+$ concentration causes slowing of $Ca^{+2}$ efflux via the $Na^+/Ca^{+2}$ exchanger and a relative increase in intracellular $Ca^{+2}$. The extra $Ca^{+2}$ increases the action potential of cardiac cells with more activation of the contractile machinery [17].

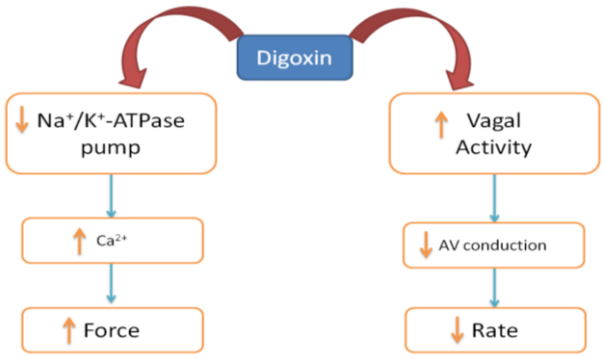


**Fig 2:** Mechanisms of action of digoxin.

The control of the ventricular rate in the setting of atrial

fibrillation has long been accomplished with digoxin. In fact, for more than 200 years, digoxin was the main agent used for this indication [18]. Clinical trials have shown that 54-70% of patients with atrial fibrillation are treated with digoxin [19, 20]. However, digoxin is not effective in controlling ventricular rate in atrial fibrillation during exercise [21]. For this reason, some guidelines recommend digoxin as second-line therapy for controlling the rate in atrial fibrillation [22]. Nevertheless, digoxin is still commonly used in this setting. Recent data have raised the question of digoxin's potential to increase the risk of strokes in patients with atrial fibrillation due to a possible role in thrombogenesis mediated through increased intracellular $Ca^{+2}$ levels [23]. This possibility could have substantial clinical implications because of the large number of such patients receiving digoxin therapy. However, more trials are needed to test this theory further. Digoxin is an appealing therapeutic option for elderly patients with atrial fibrillation because unlike other rate-control strategies (e.g., $Ca^{+2}$ channel blockers and β blockers), digoxin does not cause hypotension or have negative inotropic effects. However, caution is advised as there could be potential drug interactions with digoxin in the elderly. In a clinical trial evaluating elderly patients admitted with specific drug toxicities, those on digoxin were about 12 times as likely to have been treated with clarithromycin in the previous week [24]. Nevertheless, provided that the dosage is adjusted for renal function in elderly patients, digoxin can be inexpensive and well-tolerated therapy [25]. The treatment of heart failure is another historical use of digoxin. It has proven beneficial for symptomatic control of sinus rhythm in patients with mild to moderate heart failure. In the proved trial, digoxin therapy improved symptoms, including ejection fraction, heart rate, and exercise capacity [26]. In the radiance study, digoxin withdrawal resulted in clinical deterioration, such as reductions in systolic function and worsening of exercise tolerance [27]. However, no studies till date have shown any reduction in the incidence of mortality with the use of digoxin in patients with heart failure [4]. The most recent practice guidelines for the treatment of heart failure recommend considering the addition of digoxin in patients with persistent symptoms during therapy with an angiotensin-converting enzyme inhibitor (ACEI), a β blocker, and diuretics. Furthermore, digoxin may be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during treatment with diuretics, an ACEI, or a β blocker. Based on the results of the Digitalis Investigation Group (DIG), digoxin is currently most often used for its ability to reduce hospitalizations for declining heart failure [28]. The evaluation of the DIG trial resulted in a revision of the current perspective regarding therapeutic digoxin plasma concentrations [12, 13]. While, initially, it appeared that digoxin exhibits different effects in men and women, further analysis demonstrated that variations were more likely due to differences in the serum concentrations of digoxin [13, 29]. Digoxin serum concentrations higher than 1.2 ng/ml lead to an increased risk of mortality in patients with heart failure. Thus, the therapeutic range of digoxin concentration currently recommended for the treatment of heart failure is 0.5-0.9 ng/ml [12, 13]. Although digoxin has been historically used in the treatment of heart failure for its positive inotropic effects, it has now become apparent that the neurohormonal effects of digoxin may be equally or more important [30, 31, 32, 33]. Digoxin's effects on the autonomic nervous system improve autonomic dysfunction in heart failure, as indicated by decreases in plasma norepinephrine levels up to 42% [34]. Furthermore, digoxin has been shown to improve outcomes in patients with heart failure, even when patients remain in sinus rhythm, suggesting that the beneficial effects are unrelated to the treatment of arrhythmia.

## 5. Drug Interactions of Digoxin

Digoxin interacts with a wide variety of medications (as shown in table 1). One mechanism of drug interaction with digoxin is the change in absorption due to increased contact time in the small intestine. This can occur with concomitant use of anticholinergic agents such as atropine, diphenhydramine, phenothiazines, scopolamine, and benztropine, which slow GI motility [35]. Two other mechanisms believed to cause many drug interactions with digoxin are the inhibition of P-glycoprotein, located in the brush borders of the proximal tubule, and the inhibition of digoxin metabolism due to a lack of *Eubacterium lentum* in the GIT [8]. Antibiotics such as clarithromycin, erythromycin, and tetracycline alter the flora of the gut leading to decreased digoxin metabolism and the consequent increase in digoxin levels [8, 35]. Antiarrhythmics such as amiodarone, quinidine, and verapamil inhibit P-glycoprotein in the kidney resulting in decreased renal clearance of digoxin [35]. Digoxin can lead to life-threatening hyperkalemia, which could cause interactions with medications that also affect potassium homeostasis, such as ACEIs, angiotensin II receptor blockers (ARBs), spironolactone, eplerenone, and potassium supplements [35]. Both pharmacokinetic and pharmacodynamic mechanisms should be noted in terms of digoxin drug interactions.

**Table 1:** Potential interactions with digoxin

| | |
|---|---|
| 1. Increase Serum Levels | Amiodarone, verapamil, spironolactone, itraconazole, macrolides, tetracyclines, quinine, quinidine, cyclosporine, indomethacin, diphenoxylate, benzodiazepines, and propafenone. |
| 2. Decrease Serum Levels | Antineoplastics, activated charcoal, cholestyramine, colestipol, oral aminoglycosides, St. John's wort, rifampin, penicillamine, neomycin, metoclopramide, sulfasalazine, and $Al^{+3}$/$Mg^{+2}$ containing antacids. |
| 3. Enhance Pharmacodynamic Effects | β blockers, verapamil, diltiazem, diuretics, and sympathomimetics. |
| 4. Antagonize Pharmacodynamic Effects | Thyroid hormones. |

## 6. Risk Factors of Digoxin Toxicity

Patients at highest risk of digoxin toxicity include those with kidney failure, heart failure, and dehydration [35]. Hypokalemia, hypomagnesemia, and hypercalcemia have

also been shown to increase the risk of developing arrhythmias induced by digoxin [2, 36]. The mechanism for the increase in digoxin toxicity risk secondary to hypokalemia derives from the fact that when $K^+$ is low, more $K^+$-binding sites are open for digoxin binding, increasing the effective concentration of digoxin within the heart.

**7. Clinical Symptoms of Digoxin Toxicity**

Although digoxin toxicity may lead to the development of any type of arrhythmia, bradycardia and AV block are predicted conditions due to digoxin's mechanism of action. The inhibition of the $Na^+/K^+$-ATPase pump by digoxin leads to an increase in intracellular $Ca^{+2}$. This increase in $Ca^{+2}$ leads to an increase in the strength of contraction or inotropy. In severe toxicity, such as that seen in suicide attempts, both severe hyperkalemia and extreme bradycardia occur [2]. Hyperkalemia is a result of digoxin inhibition of the $Na^+/K^+$-ATPase activity in skeletal muscle [2, 37]. When digoxin levels in the body are elevated, side effects due to accumulation in the CNS may occur. Some of these adverse effects include blurred vision, xanthopsia (disturbances in color vision), and retrobulbar optic neuritis [2, 36]. Additional effects that may be seen because of mediation of the CNS by digoxin include nausea, vomiting, tachypnea (increased respiration rate), excitation, headache, malaise, drowsiness, dizziness, abdominal pain, confusion, hallucination, and apathy [4, 36]. Notably, cardiac symptoms of toxicity may appear before non-cardiac symptoms [36].

**8. Management of Digoxin Toxicity**

Activated charcoal (AC) can be used in the treatment of digoxin toxicity and can lead to a 30-40% drop in digoxin levels within 12-18 hours. Unlike the use of digoxin antibodies, the drop-in digoxin levels produced by activated charcoal does not completely reverse the therapeutic effects of digoxin in patients with cardiac disease [38]. This may be a beneficial strategy in patients whose digoxin concentrations do not significantly exceed those in the therapeutic range and who could benefit from conservative medical care. Additionally, supportive care involving potassium administration, discontinuation of digoxin therapy, and assessment of magnesium and calcium levels should be employed as indicated by the patient's clinical condition [38]. Digoxin immune Fab was introduced in the 1970s and is used for the treatment of life-threatening digoxin toxicity or overdose [37, 39]. The two products currently available in the U.S.A. are DigiBind and DigiFab. They are ovine in origin, collected and purified from sheep and immunized using human albumin conjugated with digoxin. Digoxin molecules bind to the antibody-fragments, making them unavailable for binding to their receptors. The digoxin-antibody complexes are then renally eliminated. The clinical conditions indicating the need for these products as defined in their package inserts include the following: acute ingestion of more than 10 mg of digoxin in adults or 4 mg of digoxin in children. Acute ingestion of digoxin leads to a serum level of more than 10 ng/ml, chronic ingestion of digoxin leads to a serum level higher than 6 ng/ml in adults or 4 ng/ml in children, or manifestations of life-threatening digoxin toxicity, such as severe ventricular arrhythmias, progressive bradycardia, second- or third-degree heart block not responsive to atropine, or serum $K^+$ levels exceeding 5 mEq/L in adults or 6 mEq/L in children with rapidly progressive symptoms of digoxin toxicity [39]. For both brands of digoxin immune Fab, one vial of the product will bind approximately 0.5 mg of digoxin. Therefore, the dose of digoxin immune Fab is based on the amount of excess digoxin believed to be present in the patient. In some cases, this amount is known, such as in the cases of suicide attempts with deliberate overdoses or unintentional ingestion by a child. However, in cases of chronic ingestion, this may be more difficult to ascertain, especially as the toxicity may have developed over time with changes in renal function. To calculate digoxin immune Fab dosage for patients experiencing acute ingestion of digoxin, one must first determine the total body load of digoxin. This can be accomplished by multiplying the amount of digoxin ingested (in mg) by the bioavailability for the product ingested (0.7 for tablets). To determine the total body load of digoxin (in mg) for patients experiencing toxicity as a result of chronic ingestion of digoxin, one should multiply the serum digoxin level (in ng/ml) by the volume of distribution of digoxin (7.3 l/kg) by the patient's ideal body weight (in kg) and divide by 1,000. Once the body load of digoxin is determined, the amount should be divided by 0.5, to account for the approximate amount of digoxin neutralized by one vial of digoxin immune Fab, to determine the number of vials of digoxin immune Fab that should be administered. An understanding of both digoxin and digoxin immune Fab pharmacokinetics is crucial for developing a therapeutic dosing regimen [37]. The volume of distribution for digoxin immune Fab is approximately 0.35 l/kg, indicating penetration into the extracellular space [39]. However, this volume is much smaller than that of digoxin, signifying that shifts from deeper tissue stores of digoxin may occur as the antibody complexes with digoxin in the central circulation as well as more accessible tissue stores [37]. The $t_{1/2}$ of digoxin immune Fab is reported to be between 15-30 hours [37, 39]. This pharmacokinetic parameter is important since if the entire dose of digoxin immune Fab is given at one time, it may be eliminated from the body before digoxin re-equilibration from deeper tissue stores, and an optimal degree of digoxin-antibody complexing can occur. For this reason, it has been recommended that half of the calculated necessary digoxin immune Fab dose be given initially, in both acute and chronic poisoning situations, followed by additional doses, administered in 1-2 hours if no clinical response is seen or in 6-12 hours if toxicity recurs [37]. The costs associated with digoxin toxicity should be considered. It has been shown that the mean overall cost associated with digoxin toxicity is approximately $4,000 per episode [40]. This cost may be somewhat variable with the use of digoxin immune Fab, especially in the treatment of patients with renal dysfunction and a serum digoxin concentration of 2.3 ng/ml or higher. In such cases, the use of digoxin immune Fab can result in a reduction in length of stay and overall lower treatment costs [41]. Because papain is used in the process of producing digoxin immune Fab, patients with hypersensitivity to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may be at risk of such a reaction. Additionally, patients with allergies to latex or dust mites may have cross-sensitivity to papain and experience hypersensitivity to digoxin immune Fab. Finally, those with allergies to sheep or ovine products or who have previously received ovine products may be at increased risk for hypersensitivity to digoxin immune Fab. The benefit of using this product in such patients should be

weighed against the risks, and as a safety measure, treatment for anaphylaxis should be readily available [39].

## 9. Conclusion

Digoxin toxicity can occur as a result of many situations, including drug interactions, electrolyte disturbances, changes in renal function, acute ingestion of large amounts of digoxin, or chronic ingestion of doses larger than necessary for therapeutic effects. Physicians should monitor patients for the symptoms of digoxin toxicity while utilizing preventive measures. Such preventive measures should include appropriate digoxin serum concentration measurements, evaluation of pharmacotherapy regimens for potential drug interactions, assessment of electrolytes, and digoxin regimen determination based on pharmacokinetic parameters. If digoxin toxicity occurs, treatment should be implemented based on the patient's clinical condition. With appropriate care, digoxin can be an efficacious, safe, and cost-effective treatment.

## 10. Conflicts of Interest

I hereby declare that there are no conflicts of interest regarding the publication of this review article.

## 11. Acknowledgement

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## 12. References

1. Smith TW, Haber E. Digitalis (first of four parts). New England Journal of Medicine. 1973; 289:945-952.
2. Rocco TP, Fang JC, Roden DM. Cardiac glycosides. In L. L. Brunton, J. S. Lazo & K. L. Parker KL (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics (11th ed). New York: McGraw-Hill, 2006, 886-889, 921-923.
3. Withering W. An account of the foxglove and some of its medical uses: With practical remarks on dropsy and other diseases. London: J and J Robinson, 1785.
4. Jortani SA, Valdes R Jr. Digoxin and its related endogenous factors. Critical Reviews in Clinical Laboratory Sciences. 2015; 34: 225-274.
5. Eichhorn EJ, Gheorghiade M. Digoxin New perspective on an old drug. New England Journal of Medicine. 2002; 347:1394-1395.
6. Winter ME. Digoxin. In M. E. Winter, ME. (Ed.), *Basic clinical pharmacokinetics* (4th ed.). Baltimore: Lippincott Williams & Wilkins, 2004, 183-221.
7. Clausen T. The Na+, K+ pump in skeletal muscle: quantification, regulation and functional significance. Acta Physiologica Scandinavica. 2014; 156:227-235.
8. Hirata S, Izumi S, Furukubo T, *et al*. Interactions between clarithromycin and digoxin in patients with end-stage renal disease. International Journal of Clinical Pharmacology and Therapeutics. 2016; 43:30-36.
9. Mutnick AH. Digoxin. In G. E. Schumacher (Ed.), Therapeutic drug monitoring (469–491). Norwalk: Appleton & Lange, 1995.
10. Gault MH, Charles JD, Sugden DI, *et al*. Hydrolysis of digoxin by acid. Journal of Pharmacy and Pharmacology. 2011; 29:27-32.
11. Gault MH, Karla J, Ahmed M, *et al*. Influence of gastric pH on digoxin biotransformation. I. Intragastric hydrolysis. Clinical Pharmacology and Therapeutics. 2012; 27:16-21.
12. Adams KF, Patterson JH, Gattis WA, *et al*. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group Trial. Journal of the American College of Cardiology. 2015; 46:497-504.
13. Rathore SS, Curtis JP, Wang Y, *et al*. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2013; 289:871-878.
14. Lewis RP. Clinical use of serum digoxin concentrations. American Journal of Cardiology. 2010; 69:97G–107G.
15. Pudek MR, Seccombe DW, Jacobson BE, Humphries K. Effect of assay conditions on cross reactivity of digoxin-like immunoreactive substance(s) with radioimmunoassay kits. Clinical Chemistry. 1985; 31:1806-1810.
16. Way BA, Wilhite TR, Miller R, *et al*. Vitros digoxin immunoassay evaluated for interference by digoxin-like immunoreactive factors. Clinical Chemistry. 2011; 44:1339-1340.
17. Rang HP, Dale MM, Ritter JM, Gardner P. Pharmacology. New York: Churchill Livingstone, 2006.
18. Khan IA, Nair CK, Singh N, *et al*. Acute ventricular rate control in atrial fibrillation and atrial flutter. International Journal of Cardiology. 2004; 97:7-13.
19. Van Gelder IC, Hagens VE, Bosker HA, *et al*. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. New England Journal of Medicine. 2002; 347:1834-1840.
20. Wyse DG, Waldo AL, DiMarco JP, *et al*. A comparison of rate control and rhythm control in patients with atrial fibrillation. New England Journal of Medicine. 2009; 347:1825-1833.
21. Beasley R, Smith DA, McHafie DJ. Exercise heart rates at different serum digoxin concentrations in patients with atrial fibrillation. The BMJ. 2013; 290:9-11.
22. Holten KB. How should we manage newly diagnosed atrial fibrillation? Journal of Family Practice. 2004; 53:641-643.
23. Chirinos JA, Castrellon A, Zambran JP, *et al*. Digoxin use is associated with increased platelet and endothelial cell activation in patients with nonvalvular atrial fibrillation. Heart Rhythm. 2005; 2:525-529.
24. Juurlink DN, Mamdani M, Kopp A, *et al*. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA. 2007; 289:1652–1658.
25. Rosenfeld LE. Atrial fibrillation: how to approach rate control. Current Cardiology Reports. 2005; 7:39-397.
26. Uretsky BF, Young JB, Shahidi FE, *et al*. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. Journal of the American College of Cardiology. 2012; 22:955-962.
27. Packer M, Gheorghiade M, Young JB, *et al*. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme

inhibitors. RADIANCE Study. New England Journal of Medicine. 1993; 329:1-7.
28. Garg R, Gorlin R, Smith T, Yusuf S. on behalf of the Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. New England Journal of Medicine. 2008; 336:525–533.
29. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. New England Journal of Medicine. 2002; 347:1403–1411.
30. Terra SG, Washam JB, Dunham GD, Gattis WA. Therapeutic range of digoxin's efficacy in heart failure: What is the evidence? Pharmacotherapy. 1999; 19:1123-1126.
31. Slatton ML, Irani WN, Hall SA, *et al*. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? Journal of the American College of Cardiology. 2014; 29:1206-1213.
32. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. Journal of the American College of Cardiology. 1992; 20:248–254.
33. Newton GE, Tong JH, Schofield AM, *et al*. Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. Journal of the American College of Cardiology. 2009; 28:155–161.
34. Krum H, Bigger T, Goldsmith RL, *et al*. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. Journal of the American College of Cardiology. 2012; 25:289-294.
35. Prybys KM. Deadly drug interactions in emergency medicine. Emergency Medicine Clinics of North America. 2004; 22:845-863.
36. Parker RB, Patterson JH, Johnson JA. Heart failure. In J. T. DiPiro, R. L. Talbert, G. C. Yee, *et al*. (Eds.), *Pharmacotherapy: A pathophysiologic approach* (6th ed., 219–260). New York: McGraw-Hill, 2005.
37. Bateman DN. Digoxin-specific antibody fragments: How much and when? Toxicological Reviews. 2004; 23:135-143.
38. Fee WH. Activated charcoal safe and effective for digoxin toxicity [letter]. American Journal of Medicine. 2008; 116:430.
39. Facts & Comparisons 4.0. (n.d.). *Digoxin immune Fab*. Retrieved December 12, 2005, from online.factsandcomparisons.com
40. Gandhi AJ, Vlasses PH, Morton DJ, Bauman JL. Economic impact of digoxin toxicity. Pharmacoeconomics. 2013; 12:175-181.
41. DiDomenico RJ, Walton SM, Sanoski CA, Bauman JL. Analysis of the use of digoxin immune fab for the treatment of non-life-threatening digoxin toxicity. Journal of Cardiovascular Pharmacology and Therapeutics. 2017; 5:77-85.