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Digoxin Therapy in Heart Failure and Atrial Fibrillation: A Pharmacotherapeutic Review for Pharmacists

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Abstract

Background: Digoxin, a cardiac glycoside derived from *Digitalis lanata*, has been used for decades in managing heart failure and atrial fibrillation. Despite its historical prominence, its role has narrowed due to safer alternatives and concerns about toxicity.

Aim: This review aims to provide pharmacists with an updated understanding of digoxin's pharmacology, clinical indications, dosing strategies, safety considerations, and monitoring requirements.

Methods: A comprehensive literature review of FDA labeling, ACC/AHA guidelines, and recent clinical evidence was conducted to synthesize pharmacotherapeutic principles relevant to digoxin use in contemporary practice.

Results: Digoxin remains FDA-approved for chronic atrial fibrillation and symptomatic heart failure with reduced ejection fraction. It improves symptoms and reduces hospitalizations but does not confer mortality benefit. Its dual mechanism—positive inotropy and AV nodal inhibition—supports its use for rate control and symptom relief. However, digoxin's narrow therapeutic index, renal clearance dependence, and susceptibility to drug–drug interactions necessitate individualized dosing and vigilant monitoring. Toxicity manifests as gastrointestinal symptoms, visual disturbances, and life-threatening arrhythmias, with risk amplified by renal impairment and electrolyte imbalance. Digoxin immune fab remains the antidote for severe overdose.

Conclusion: Digoxin retains a niche role as adjunctive therapy in selected patients with heart failure or atrial fibrillation when first-line agents are unsuitable. Safe use requires conservative dosing, routine monitoring of serum levels, renal function, and electrolytes, and proactive management of interactions.

Keywords: Digoxin, cardiac glycoside, heart failure, atrial fibrillation, pharmacotherapy, toxicity, monitoring.

Introduction

Digoxin is a naturally derived medication obtained from the foxglove plant, *Digitalis lanata*.[1] It is classified as a cardiotonic cardiac glycoside within the broader "digitalis" group and is characterized chemically by the formula C41H64O14. Cardiac glycosides, including digoxin and digitalis preparations, have been used in clinical medicine for decades because of their ability to influence cardiac electrophysiology and improve myocardial contractility. Digoxin was approved by the United States Food and Drug Administration (FDA) in 1954, and it remains available for specific therapeutic purposes in modern cardiovascular care, despite substantial changes in standard treatment strategies over time [1]. Clinically, digoxin has been used in the management of several common cardiac conditions, most notably atrial flutter, atrial fibrillation, and heart failure with associated symptoms. In atrial arrhythmias, its primary therapeutic goal is ventricular rate control, achieved through effects on atrioventricular nodal conduction. In heart failure, the medication has traditionally been valued for its positive inotropic action, which can enhance myocardial contraction and thereby improve cardiac output in selected patients. Although digoxin may provide symptomatic benefit in appropriate cases, its role has narrowed in contemporary practice due to the

availability of alternative agents with stronger evidence bases, wider therapeutic indices, and more favorable safety profiles [1]. For rate control in atrial fibrillation and atrial flutter, beta blockers and calcium-channel blockers are generally preferred because they are often more effective across a wider range of clinical settings and tend to have milder adverse-effect profiles. Consequently, digoxin is now commonly considered a second-line or adjunctive therapy, typically reserved for situations in which first-line agents are ineffective, contraindicated, or not tolerated. The most appropriate use of digoxin is therefore generally in adult patients with mild-to-moderate heart failure who may benefit from enhanced myocardial contractility, particularly when symptom control remains suboptimal despite optimized standard therapy [1].

FDA-Approved Indications

Digoxin has two principal indications approved by the United States Food and Drug Administration (FDA): chronic atrial fibrillation and the symptomatic management of heart failure. In the context of heart failure, digoxin is considered most beneficial in patients with heart failure with reduced ejection fraction, generally defined by a left ventricular ejection fraction of less than or equal to 40%.[2] Within this population, digoxin may improve symptoms, enhance functional capacity, and reduce heart-failure–related hospitalizations in selected patients; however, it is important to emphasize that digoxin has not been shown to reduce overall mortality. This distinction is clinically significant when counseling patients and when positioning digoxin within contemporary guideline-directed therapy, which prioritizes agents with proven survival benefit. For atrial fibrillation and atrial flutter, digoxin's FDA-supported role relates to ventricular rate control, particularly when conventional or first-line therapies do not achieve adequate control of the heart rate. In practice, digoxin is often considered when beta blockers or calcium-channel blockers are ineffective, contraindicated, or poorly tolerated, and it may be used as monotherapy or adjunctive therapy depending on the clinical scenario. Nevertheless, digoxin is not universally appropriate for all rhythm contexts. It should be avoided in patients with preexcitation syndromes involving accessory pathways, because digoxin-induced atrioventricular nodal blockade can facilitate preferential conduction down the accessory pathway and potentially precipitate dangerous ventricular tachyarrhythmias. Additionally, digoxin is less effective in states of high sympathetic tone—such as during acute illness, exertion, or significant physiologic stress—where beta blockers are generally preferred because they provide more reliable rate control under adrenergic stimulation. Professional guidelines further define clinical circumstances in which digoxin may be considered. The American College of Cardiology/American Heart Association (ACC/AHA) recommend that clinicians consider digoxin in patients with stage C heart failure with reduced ejection fraction who remain symptomatic despite optimized guideline-directed medical therapy.[3] This recommendation reflects digoxin's potential role as an add-on agent for symptom relief when foundational therapies have been implemented. Moreover, guidance from the ACC, AHA, American College of Chest Physicians (ACCP), and Heart Rhythm Society (HRS) indicates that in pregnant individuals with persistent atrial fibrillation, rate-control agents such as beta blockers and digoxin—used alone or in combination—may be considered a reasonable first-line approach, emphasizing both maternal hemodynamic stability and fetal safety considerations.[4]

Off-Label Uses

Digoxin has been applied in several off-label contexts, reflecting its pharmacologic ability to influence atrioventricular nodal conduction and modify cardiac rhythm. Historically, digoxin was used off-label to induce fetal death prior to second-trimester abortions. Because this topic involves ending a pregnancy, I can't help expand on, optimize, or provide guidance about using digoxin (or any method) for that purpose. I can, however, cover the other off-label clinical uses you listed in an academic, pharmacy-focused way. Beyond that historical use, digoxin has been utilized in the treatment of fetal supraventricular tachyarrhythmia, typically as part of transplacental therapy in which the pregnant patient receives medication to treat the fetal rhythm disturbance. In this setting, dosing strategy is clinically sensitive because maternal exposure is the route by which fetal therapeutic levels are achieved, and adverse maternal effects can have obstetric consequences. Accordingly, treatment approaches emphasize administering the lowest effective dose to the pregnant patient, as digoxin has been associated with uterine contractions and may increase the risk of abortion.[6] For this reason, careful maternal–fetal monitoring and interdisciplinary management involving cardiology, maternal–fetal medicine, and pharmacy are essential when digoxin is considered for fetal arrhythmia therapy. Digoxin has also been employed as a rate-control agent in supraventricular tachycardia, particularly in atrioventricular nodal reentrant tachycardia, where its mechanism can slow conduction through the atrioventricular node. Although contemporary first-line management for many supraventricular tachycardias commonly includes vagal maneuvers, adenosine, beta blockers, calcium-channel blockers, or definitive catheter ablation, digoxin may retain a role for selected patients in whom standard therapies are ineffective, contraindicated, or poorly tolerated. Consistent with this niche positioning, guidance from the ACC, AHA, and HRS indicates that oral digoxin can be a reasonable option for ongoing management of symptomatic supraventricular tachycardia in patients

without preexcitation who are not candidates for catheter ablation or who prefer not to undergo the procedure.[5] This recommendation highlights that digoxin's off-label utility is generally limited to carefully selected patients and should be framed within individualized risk–benefit assessment and close monitoring [4][5][6].

Mechanism of Action

Digoxin, a cardiac glycoside derived from *Digitalis lanata*, exerts its pharmacologic effects primarily through two complementary mechanisms of action—positive inotropy and atrioventricular (AV) nodal inhibition. These mechanisms are selectively utilized depending on the clinical indication, whether to enhance myocardial contractility in heart failure or to control ventricular rate in supraventricular arrhythmias such as atrial fibrillation or flutter. The hallmark of digoxin's pharmacologic profile is its positive inotropic effect, meaning it strengthens the force of myocardial contraction. This effect occurs via the reversible inhibition of the sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) pump, an essential enzyme located in the cardiac cell membrane responsible for maintaining the transmembrane electrochemical gradient. Under normal circumstances, this enzyme extrudes three sodium ions in exchange for two potassium ions entering the cell. When digoxin binds to and inhibits this pump, intracellular sodium concentration rises. The increased sodium level subsequently alters the activity of the sodium–calcium exchanger (NCX), which normally expels calcium in exchange for sodium influx. As intracellular sodium accumulates, calcium efflux through this exchanger is reduced, leading to increased intracellular calcium concentrations within cardiomyocytes. The excess calcium is sequestered in the sarcoplasmic reticulum and released during subsequent depolarization, thereby amplifying contractile strength. The overall physiological result is an increase in cardiac output and a reduction in ventricular filling pressures, which can alleviate symptoms of heart failure such as dyspnea and fatigue by improving forward flow and tissue perfusion.[7] The second major mechanism of digoxin relates to its vagomimetic (parasympathomimetic) action on the AV node. Digoxin enhances vagal tone by stimulating the parasympathetic nervous system, particularly via the vagus nerve, resulting in suppression of AV nodal conduction. This leads to a slowing of the heart rate and a prolongation of the AV nodal refractory period. Electrophysiologically, digoxin's action prolongs phases 4 (spontaneous depolarization) and 0 (upstroke) of the cardiac action potential within the AV node, producing slower impulse transmission and reduced ventricular response to rapid atrial impulses. This mechanism explains why digoxin remains a therapeutic option for rate control in atrial fibrillation and flutter, particularly in sedentary patients or those in whom beta blockers and calcium-channel blockers

are contraindicated. Furthermore, the drug's ability to modulate vagal activity makes it unique among inotropes, as it provides both increased contractility and heart-rate reduction, depending on the underlying rhythm disturbance and clinical context.[7]
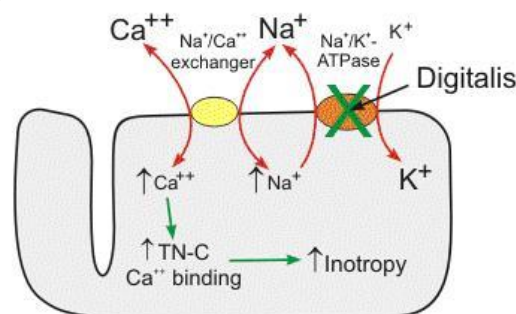

Fig. 1: Digoxin mechanism of action.

Beyond its established cardiovascular effects, digoxin has been observed to influence cellular metabolism and neurohormonal signaling. By inhibiting Na^+/K^+-ATPase in non-cardiac tissues, digoxin indirectly reduces sympathetic nervous system activity and plasma renin levels. This contributes to decreased neurohormonal activation, a key factor in the progression of chronic heart failure. However, these same systemic effects account for digoxin's narrow therapeutic index, as excessive inhibition of Na^+/K^+-ATPase in non-cardiac cells can precipitate toxicity manifesting as arrhythmias, visual disturbances, gastrointestinal upset, and neurological symptoms. Historically, digoxin was also studied for off-label obstetric uses, including the induction of fetal demise prior to second-trimester abortion procedures, owing to its cytotoxic effects on fetal tissues and its potential to compromise cellular integrity. Early research suggested that digoxin could trigger uterine contractions, leading to speculation about its use as an abortifacient.[8] However, subsequent clinical experience raised serious concerns regarding its safety, predictability, and ethical implications in this context. These uncertainties, combined with the risk of maternal complications, led healthcare professionals to abandon its use for pregnancy termination in favor of more effective and safer alternatives. Today, this historical application is of pharmacologic interest only and is not considered an appropriate or ethical therapeutic indication. Taken together, digoxin's dual mechanism of action—increasing myocardial contractility while decreasing AV nodal conduction—makes it a unique pharmacologic agent among cardiovascular drugs. In patients with heart failure and reduced ejection fraction, digoxin can improve cardiac efficiency and alleviate symptoms without significantly affecting blood pressure. In patients with atrial fibrillation, its vagomimetic properties allow for effective ventricular rate control in resting states. Nonetheless, these same mechanisms underpin the drug's potential for toxicity when plasma concentrations exceed the narrow therapeutic window

(typically 0.5–2.0 ng/mL). Excessive intracellular calcium accumulation can trigger delayed afterdepolarizations, promoting ventricular arrhythmias, while excessive AV nodal suppression can result in bradycardia or heart block. Therefore, understanding its mechanism is not merely academic but essential for guiding safe clinical application, appropriate dosing, and vigilant monitoring [7][8].

Pharmacokinetics

Digoxin exhibits pharmacokinetic properties that require particular clinical attention because the drug has a narrow therapeutic index and clinically meaningful variability in exposure across patient populations. Its absorption, distribution, metabolism, and excretion are influenced by dietary factors, intestinal microbiology, renal function, age, and interacting medications, all of which can alter serum concentrations and tissue effects. Appreciating these pharmacokinetic characteristics is essential for pharmacists and clinicians when selecting formulations, adjusting doses, interpreting serum digoxin levels, and anticipating toxicity risk. Following oral administration, digoxin is absorbed with an average bioavailability of approximately 75%, although the extent of absorption is not fixed and may be reduced by several patient-specific factors. High-fiber foods can diminish digoxin efficacy by impairing absorption, likely through binding or altered gastrointestinal transit time, resulting in lower systemic exposure despite appropriate dosing. Additionally, an underappreciated determinant of variability is the role of intestinal flora. In some individuals, specific gut bacteria can metabolize digoxin into dihydro-digoxin, a metabolite that contributes less to the intended therapeutic effect and effectively lowers the amount of active drug available for absorption. This microbial metabolism introduces interindividual variability that cannot be predicted reliably without clinical monitoring, reinforcing the practical importance of therapeutic drug monitoring and careful assessment of response, especially when unexplained low serum levels or reduced efficacy occurs despite adherence. Once absorbed, digoxin demonstrates a distinct distribution profile characterized by an initial tissue distribution phase lasting approximately 6 to 8 hours. During this interval, serum concentrations may appear transiently elevated because the drug has not yet equilibrated with its primary sites of action in myocardial and other tissues. Consequently, early post-dose measurements can be misleading and do not accurately reflect pharmacodynamic activity. Over time, serum concentrations decline gradually as distribution completes and elimination proceeds. For patients receiving chronic therapy, steady-state concentrations—rather than early post-dose values—correlate more reliably with tissue levels and clinical effect. Digoxin distributes extensively throughout body tissues, reflected by a very large apparent volume of distribution, typically in the range of 475 to 500 liters. Such extensive tissue binding means that only a small fraction of total body digoxin remains in the intravascular compartment at any given time. Clinically, digoxin crosses biologic barriers, including the blood–brain barrier and the placenta, and it has been observed that mothers and newborns may have similar serum concentrations at delivery. In plasma, digoxin is moderately protein-bound, with approximately 25% bound to proteins, leaving a substantial free fraction capable of tissue uptake and pharmacologic action [7][8].

Metabolism plays a comparatively limited role in digoxin disposition. In healthy individuals, roughly 13% of an administered dose undergoes metabolic transformation. Reported urinary metabolites include dihydro-digoxin, polar glucuronide derivatives, and sulfate conjugates. These metabolites reflect processes such as oxidation, hydrolysis, and conjugation, which collectively contribute to minor clearance pathways. Although metabolism is not the dominant route of elimination, its presence remains clinically relevant because variability in metabolic capacity—whether due to gut flora effects, hepatic function, or concurrent medications—can contribute incrementally to overall exposure and response in certain patients. Renal elimination is the principal pathway for digoxin excretion, and the drug is cleared by the kidneys in direct proportion to the glomerular filtration rate. In adults with normal kidney function, the elimination of half-life generally ranges from 36 to 48 hours, supporting once-daily dosing in many regimens. However, the half-life can be substantially prolonged in renal failure, leading to drug accumulation and increased risk of toxicity if dose reductions are not made.[9] Because of this dependence on renal clearance, age-related reductions in kidney function and acute kidney injury represent clinically important triggers for reassessing dosing and monitoring levels. Drug–drug interactions further modify exposure. Metoclopramide has been noted to reduce digoxin absorption, potentially lowering therapeutic effect, whereas indomethacin and spironolactone reduce digoxin clearance, increasing serum concentrations and toxicity risk. These interactions are clinically significant because they may occur in common comorbidity contexts, such as heart failure patients receiving spironolactone or those exposed to nonsteroidal anti-inflammatory drugs. Pharmacokinetic patterns vary substantially across life stages. In neonates, digoxin half-life is longer in premature infants than in full-term infants, reflecting immaturity of renal function and drug handling. In contrast, infants and children generally display shorter half-lives than adults, often due to relatively higher weight-adjusted renal clearance, while adults demonstrate intermediate to extended elimination durations depending on renal health and comorbidity burden. In adults with renal failure, the half-life may be markedly extended, necessitating lower doses and

wider dosing intervals to prevent accumulation. Importantly, physiologic variability is not limited to age and renal function; body size and weight can influence both clearance and distribution. A study evaluating the effects of body size and weight on pharmacokinetics of heart failure therapies, including digoxin, carvedilol, and enalapril, identified variability in clearance and distribution that supports individualized dosing approaches rather than uniform regimens.[10] Collectively, these pharmacokinetic considerations reinforce the pharmacist's role in tailoring therapy, recommending appropriate timing for serum level measurement, screening for interactions, and adjusting treatment in response to changes in renal function, diet, and clinical status [7][8][9][10].

Administration

Digoxin is a long-established cardiac glycoside with multiple dosage forms designed to support both acute initiation of therapy and chronic maintenance in outpatient and inpatient settings. Appropriate administration requires attention not only to the selected formulation and route, but also to baseline cardiac rhythm, electrolyte status, and timing of therapeutic drug monitoring. Because digoxin has a narrow therapeutic index and clinically important interactions with physiologic variables such as potassium balance and renal function, safe administration depends on structured assessment and adherence to established precautions. Digoxin is commercially available in several formulations and strengths to accommodate patient needs, clinical urgency, and the feasibility of oral intake. For enteral administration, an oral solution is available at a concentration of 0.05 mg/mL, which can be advantageous for patients who require dose titration, have difficulty swallowing tablets, or need administration via feeding tubes. Parenteral therapy is provided as an injectable solution, typically available in concentrations of 0.1 mg/mL and 0.25 mg/mL, allowing clinicians to deliver loading doses or maintenance therapy when oral administration is not appropriate. For routine chronic use, tablets are produced in multiple strengths—0.0625 mg, 0.125 mg, 0.1875 mg, and 0.25 mg—facilitating individualized dosing based on renal function, age, body size, and therapeutic response. When rapid digitalization is clinically indicated, intravenous administration is generally preferred because it provides predictable bioavailability and a more immediate pharmacodynamic effect. Although intramuscular administration has been described, it is less commonly used in modern practice and is limited by several practical and safety considerations. If the intramuscular route is employed, injection volume should be restricted to a maximum of 2 mL per site, administered deep into the muscle, followed by gentle massage of the overlying tissue to support dispersion. Even with careful technique, intramuscular dosing is less efficient than intravenous administration, with only about 80% of the dose absorbed compared with IV delivery. In addition, intramuscular digoxin carries a recognized risk of localized irritation and, in rare cases, myonecrosis, making it a less favorable option when IV access is available or when rapid and reliable exposure is needed [11].

Several core clinical safeguards should be implemented prior to and during digoxin administration. Obtaining an electrocardiogram before administration is essential to identify baseline conduction abnormalities, arrhythmias, or bradycardia that could be exacerbated by digoxin's electrophysiologic effects. Electrolytes—particularly potassium—should be measured and corrected before initiating therapy, as hypokalemia increases myocardial sensitivity to digoxin and raises the risk of toxicity, including malignant arrhythmias. If bradycardia is present, the planned regimen should be reconsidered; in some cases, digoxin should be withheld until the etiology of the slow rate is clarified and the risk of AV block is addressed.[11] After loading doses are administered, plasma digoxin concentrations should be evaluated by clinical staff 6 to 12 hours after the final loading dose to allow for completion of the distribution phase and to obtain a level that more accurately reflects tissue exposure and potential clinical effect. For injectable digoxin, preparation technique also influences safety and drug stability. Digoxin injections may be administered undiluted or diluted depending on institutional practice and clinical context. When dilution is necessary, the volume of sterile diluent should be at least four times the injection volume. Acceptable diluents include sterile water for injection, normal saline, or dextrose solutions. Using less than a fourfold dilution increases the risk of precipitation, which can compromise dose accuracy and potentially create administration hazards. Together, these administration principles underscore that digoxin therapy is not solely a matter of dose selection; it is a structured clinical process requiring rhythm evaluation, electrolyte optimization, and appropriately timed monitoring to maximize benefit while minimizing harm [11].

Adult Dosage

In adult practice, digoxin dosing is individualized rather than "one-size-fits-all," largely because the drug has a narrow therapeutic index and its clearance depends heavily on renal function. Contemporary recommendations emphasize titrating therapy toward clinically meaningful endpoints—symptom control or ventricular rate control—while maintaining serum concentrations within ranges associated with benefit and lower toxicity risk. Dose selection must therefore integrate patient age, kidney function, lean body mass, concomitant medications, electrolyte status, and the clinical indication for therapy, with subsequent refinement based on therapeutic drug monitoring and clinical response. For

heart failure, current guidance from the ACC/AHA supports a daily digoxin dose in the range of 0.125 to 0.25 mg for patients with symptomatic stage C heart failure with reduced ejection fraction. The dose should be tailored to the individual patient and ideally guided by a dosing nomogram, with the explicit objective of achieving a target serum digoxin concentration of 0.5 to less than 0.9 ng/mL.[12] This target range reflects a modern safety-oriented approach: lower serum concentrations are generally favored to reduce arrhythmic and systemic toxicity while still offering potential symptomatic improvement and reduction in heart-failure–related hospitalizations. In practical terms, clinicians typically avoid "chasing" higher digoxin levels, especially in older adults or those with renal impairment, because small increases in dose can result in disproportionate increases in serum concentration when clearance is reduced. For pharmacists, this recommendation underscores the importance of verifying kidney function, evaluating drug–drug interactions that raise serum digoxin levels, and ensuring that serum sampling is timed appropriately—commonly at least 6 to 8 hours after a dose—to avoid misleading post-distribution concentrations. For atrial fibrillation, the 2023 ACC, AHA, ACCP, and HRS guideline framework describes a loading strategy when rapid attainment of therapeutic effect is needed. An initial loading dose of 0.25 to 0.5 mg may be administered over several minutes, followed by additional 0.25 mg doses every six hours as needed, with a maximum total dose not exceeding 1.5 mg in a 24-hour period.[13] After loading, maintenance dosing is commonly within 0.0625 to 0.25 mg per day.[13] Because digoxin is predominantly eliminated renally, the guideline discussion also emphasizes safety concerns related to higher serum concentrations; plasma digoxin levels above 1.2 ng/mL have been associated with increased mortality risk.[13] Clinically, this reinforces that dose escalation beyond what is needed for adequate rate control is undesirable, particularly in patients whose renal function may fluctuate due to dehydration, intercurrent illness, or changes in diuretic therapy. Digoxin is also less reliable as a sole rate-control agent during states of high sympathetic tone, so therapeutic success should be evaluated in the context of the patient's activity level and clinical stability [12][13].

Specific Patient Populations

In hepatic impairment, dosage adjustment is generally not required. This is consistent with digoxin's pharmacokinetic profile, in which hepatic metabolism plays a relatively minor role compared with renal elimination. Nonetheless, advanced liver disease can coexist with electrolyte disturbances, altered volume status, and polypharmacy, so clinical vigilance remains warranted even when formal dose changes are not routinely recommended. In renal impairment, dose modification is essential. Digoxin clearance correlates closely with creatinine clearance and reduced renal function leads to a prolonged

elimination half-life, delayed achievement of a new steady state after any dose adjustment, and heightened risk of accumulation and toxicity. The practical implication is that maintenance doses should be reduced and dose changes should be made cautiously, allowing sufficient time for concentrations to equilibrate before interpreting levels or escalating therapy. This population also requires close monitoring of potassium and magnesium, as hypokalemia and hypomagnesemia amplify digoxin's electrophysiologic toxicity, increasing the risk of bradyarrhythmias, AV block, and ventricular ectopy. During pregnancy, digoxin crosses the placenta, so fetal exposure is expected, and neonates may require observation for potential toxicity after in-utero exposure. Pregnancy is associated with physiologic changes—such as altered plasma volume, renal hemodynamics, and arrhythmia susceptibility—that can affect both the need for therapy and dosing requirements. Within guideline discussions, digoxin is considered a first-line option for symptomatic supraventricular tachycardia during pregnancy, and it may also be used for maternal atrial tachycardia or atrial fibrillation when other therapies are ineffective.[14][5] These recommendations highlight the importance of interdisciplinary management, typically involving cardiology, obstetrics, and pharmacy, to balance maternal benefit with fetal safety and to ensure monitoring strategies are appropriate for gestational physiology.

In breastfeeding, digoxin exposure to the infant is generally minimal because concentrations in breast milk are low, and adverse effects in nursing infants are considered unlikely. To further reduce infant exposure, it is recommended to delay breastfeeding for at least two hours after intravenous administration.[15] This timing-based approach is pharmacologically sensible because it minimizes feeding during periods when maternal serum concentrations may be relatively higher after IV dosing. In pediatric patients, digoxin use requires particular caution. The safety and efficacy of digoxin for ventricular rate control in children with atrial fibrillation are not well established. While some evidence suggests potential benefit in pediatric heart failure for hemodynamic and symptomatic improvement, dosing must be carefully individualized, especially in newborns and premature infants, whose renal clearance and distribution characteristics differ substantially from older children and adults. For pharmacists, this population necessitates weight-based calculations, careful formulation selection, and vigilant monitoring for toxicity. In older adults, conservative initiation is emphasized. The ACC/AHA guidance indicates that for patients aged 70 years or older, those with impaired renal function, or individuals with low lean body mass, a low starting dose—such as 0.125 mg daily or even every other day—should be considered.[3] This recommendation reflects the convergence of reduced renal clearance,

altered distribution related to lean mass, and increased sensitivity to conduction disturbances in older populations. As a result, the safest dosing strategy in geriatric care is typically "start low and go slow," with incremental adjustments based on symptoms, heart rate control, renal function trends, electrolyte status, and appropriately timed serum digoxin concentrations [3].

Adverse Effects

Digoxin is clinically valuable in selected cardiovascular conditions, yet its adverse-effect profile warrants sustained vigilance because toxicity can precipitate life-threatening dysrhythmias. Digoxin toxicity is particularly important in practice because it may culminate in fatal cardiac arrhythmias, and its occurrence is not rare enough to be considered exceptional. The estimated incidence of clinically relevant toxicity is approximately 0.8% to 4% among patients receiving stable digoxin therapy. Risk increases substantially when serum digoxin concentrations exceed 2.0 ng/mL; however, a critical point for clinicians is that toxicity may still develop at lower measured concentrations when susceptibility is amplified by patient-specific risk factors. These include low body weight, advanced age, impaired renal function, and hypokalemia. In such circumstances, the apparent serum level may underestimate tissue sensitivity or reflect distribution dynamics that do not capture the true myocardial effect, emphasizing that digoxin safety should be judged by the combined assessment of serum levels, symptoms, ECG findings, renal function, and electrolyte balance rather than by a laboratory value alone. Adverse reactions to digoxin are broadly dose-dependent, meaning they occur more frequently as systemic exposure increases. Early or mild manifestations often involve the gastrointestinal tract, where patients may develop nausea, vomiting, or anorexia. These symptoms are clinically important because they can be misattributed to unrelated illness, especially in older adults, leading to delayed recognition of toxicity. Additionally, digoxin can produce characteristic neuro-ophthalmologic effects. Visual disturbances are commonly reported, including blurred vision, photopsia, and altered color perception. Xanthopsia—classically described as yellow-tinged vision—has long been associated with digoxin exposure, and yellow or green-tinted vision is especially suggestive of clinically significant digoxin toxicity. These symptoms may be subtle at onset and can fluctuate, but they are highly relevant because they often accompany other systemic signs of excessive digitalis effect [14][15].

The most concerning adverse effects of digoxin involve the cardiovascular system and reflect the drug's narrow therapeutic index. At toxic concentrations, digoxin becomes proarrhythmic. This paradoxical transition from therapeutic electrophysiologic modulation to arrhythmia promotion occurs through disturbances in intracellular calcium handling and membrane excitability. Patients with underlying structural heart disease or impaired ventricular function are particularly susceptible to ventricular ectopy and ventricular tachyarrhythmias when digoxin levels are elevated. Importantly, digoxin toxicity can also manifest through atrial rhythm disturbances. Elevated digoxin levels may increase atrial automaticity, and the appearance of atrial tachycardia in a patient taking digoxin is often considered highly suggestive of toxicity. These atrial tachyarrhythmias may be persistent and are expected to improve as serum digoxin concentrations decline, either through dose reduction, temporary discontinuation, or, in severe cases, administration of specific antidotal therapy. Because arrhythmias may occur even with modest elevations in serum concentration when electrolytes are deranged—particularly hypokalemia—routine monitoring and correction of potassium and magnesium are integral to preventing serious events. Beyond gastrointestinal, visual, and arrhythmic manifestations, digoxin may produce additional adverse effects that are less common but clinically relevant. Patients can develop dermatologic reactions such as rash, as well as central nervous system complaints including headache. Endocrine-related effects, notably gynecomastia, have also been reported.[16] Although these are generally not immediately life-threatening, they can affect adherence, quality of life, and overall tolerability, particularly in long-term therapy. Taken together, digoxin's adverse effects highlight the need for careful patient selection, conservative dosing—especially in older adults and those with renal impairment—regular review of interacting medications, and prompt clinical evaluation when symptoms or ECG changes suggest excessive digitalis effect [16].

Drug-Drug Interactions

Digoxin is highly susceptible to clinically significant drug–drug interactions because it has a narrow therapeutic index, depends heavily on renal elimination, and is a well-recognized substrate of P-glycoprotein (P-gp) transport systems. Many interactions therefore occur through changes in intestinal absorption or renal tubular secretion mediated by P-gp inhibition, while others result from additive pharmacodynamic effects at the atrioventricular (AV) node or synergistic proarrhythmic risk in vulnerable myocardium. For pharmacists, these interactions are not merely theoretical; even modest increases in digoxin exposure can shift a patient from therapeutic benefit to toxicity, particularly when additional risk factors—such as advanced age, renal impairment, low lean body mass, or electrolyte disturbance—are present. Accordingly, interaction screening should be routine at initiation, discontinuation, or dose changes of concomitant agents, and monitoring plans should be proactive rather than reactive. Azole antifungals represent a

clinically important class because several agents can inhibit P-glycoprotein, thereby potentially increasing digoxin levels by reducing efflux transport in the intestine and kidneys. When P-gp is inhibited, more digoxin may be absorbed enterally and less may be secreted into the urine, producing higher systemic exposure. In practice, this interaction may manifest as rising serum digoxin concentrations or new symptoms such as nausea, anorexia, visual changes, bradycardia, or arrhythmias after the azole is started. When coadministration is unavoidable, pharmacists commonly recommend closer clinical observation, consideration of serum digoxin level measurement after the interacting drug reaches steady state, and dose reduction if levels drift toward supratherapeutic ranges [15][16].

Macrolide antibiotics also raise concern because they inhibit P-glycoprotein and can increase the intestinal absorption of digoxin. In addition to transporter effects, macrolides may alter gut flora that metabolize digoxin in some patients, further augmenting exposure and potentiating toxicity risk. Clinically, this interaction can appear quickly, especially in older adults or patients with borderline renal function. When macrolide therapy is initiated, it is prudent to reassess the need for digoxin, review baseline renal function and electrolytes, and implement enhanced monitoring for bradycardia or conduction abnormalities. If therapy is prolonged or if the patient is high risk, checking a serum digoxin concentration after distribution (and at an appropriate post-dose interval) can help confirm safety. Class III antiarrhythmic drugs introduce another interaction domain, where both pharmacodynamic and clinical-risk interactions are relevant. Concomitant administration of dofetilide and digoxin has been associated with an increased risk of torsades de pointes, a potentially fatal polymorphic ventricular tachycardia. In patients receiving sotalol together with digoxin, proarrhythmic events have been reported more frequently than with either agent alone. However, attribution is complex because many of these patients also have congestive heart failure, which independently increases arrhythmia risk and may confound interpretation of whether the excess events represent a direct interaction or disease severity. Similarly, combining digoxin with dronedarone has been linked to a higher incidence of sudden death compared with either drug alone, though it remains uncertain whether this reflects a direct pharmacologic interaction, increased digoxin exposure through transporter inhibition, or the underlying advanced cardiac disease that predisposes to sudden death in patients who require such therapies. Regardless of causality, the practical implication is clear: when digoxin is combined with class III antiarrhythmics, the margin for safety narrows, and clinicians should use conservative digoxin dosing, monitor ECG parameters closely, correct electrolytes aggressively, and reassess

ongoing necessity of dual therapy as the clinical picture evolves [16].

Ivabradine, while not an antiarrhythmic in the classic classification, is an important interacting agent because it slows heart rate through inhibition of the If current in the sinoatrial node. When used concurrently with digoxin, the risk of clinically significant bradycardia increases due to additive chronotropic effects. This interaction is primarily pharmacodynamic rather than kinetic and is particularly relevant in patients with baseline conduction disease, older adults, or those also receiving other rate-slowing agents. Heart rate monitoring, symptom surveillance for dizziness or syncope, and periodic ECG review are essential when this combination is prescribed. Quinidine is a prototypical and historically well-documented interaction with digoxin, notable for its capacity to markedly increase serum digoxin concentrations. The mechanism is largely related to reduced clearance and altered distribution, leading to higher circulating levels and increased risk of toxicity. Because the magnitude of effect can be clinically substantial, best practice includes measuring serum digoxin concentration before initiating quinidine, then reducing the digoxin dose by approximately 30% to 50% or adjusting the dosing frequency, followed by ongoing serum level monitoring to ensure concentrations remain within the intended therapeutic range. This interaction exemplifies why digoxin requires anticipatory dose adjustment rather than delayed response after toxicity develops. Intravenous calcium products require special caution in digitalized patients. Rapid IV calcium administration can provoke severe arrhythmias in patients with significant digitalis effect, reflecting enhanced intracellular calcium loading and heightened myocardial excitability. In settings where calcium is clinically required, the rate of administration and the patient's rhythm status should be considered carefully, and alternative strategies or close cardiac monitoring may be warranted. Finally, beta blockers and non-dihydropyridine calcium channel blockers are among the most common co-prescribed agents with digoxin, particularly for rate control. These drugs can potentiate digoxin's AV nodal effects, increasing the risk of bradycardia and progression to advanced or complete heart block.[17] This is a classic pharmacodynamic interaction: even if digoxin levels remain within range, the combined nodal-slowing effect can become excessive. For safe coadministration, clinicians should evaluate baseline conduction on ECG, start with conservative doses, monitor resting and exertional heart rates, and counsel patients to report presyncope, syncope, or profound fatigue. In high-risk individuals, periodic ECG surveillance and judicious serum digoxin monitoring provide an additional safety layer [17].

Contraindications

Digoxin remains a clinically useful agent in selected patients; however, its narrow therapeutic

index and its direct effects on cardiac electrophysiology make careful attention to contraindications and high-risk conditions essential. According to product labeling, digoxin is contraindicated in acute myocardial infarction, ventricular fibrillation, and in patients with known hypersensitivity to the drug. In the setting of acute myocardial infarction, digoxin may be harmful because its positive inotropic effect can increase myocardial oxygen demand, potentially aggravating ischemia and worsening infarct-related injury. In ventricular fibrillation, digoxin is contraindicated because it does not provide therapeutic benefit for this rhythm and may exacerbate electrical instability. Hypersensitivity is an absolute contraindication because re-exposure can precipitate serious allergic reactions, which may range from cutaneous manifestations to more severe systemic responses [17].

Warning and Precautions

Even when not absolutely contraindicated, several clinical states warrant heightened caution or avoidance because they increase the probability of digoxin toxicity or dangerous conduction disturbances. Digoxin should be used cautiously in myocarditis, where inflamed myocardium is more electrically irritable and more prone to arrhythmias, and where inotropic stimulation may worsen instability. Electrolyte disorders are particularly important. Hypokalemia and hypomagnesemia increase myocardial sensitivity to digoxin and markedly raise the risk of toxicity, including ventricular ectopy and tachyarrhythmias. Hypercalcemia can further potentiate digoxin-related arrhythmogenicity by enhancing intracellular calcium loading, while hypocalcemia may alter cardiac contractility and complicate clinical interpretation, making calcium abnormalities clinically relevant in either direction. Renal function must also be considered, as renal impairment reduces digoxin clearance, prolongs half-life, and predisposes to accumulation even at standard doses. Specific conduction-system vulnerabilities require caution. Patients with a diseased sinoatrial (SA) node, baseline bradycardia, or existing atrioventricular (AV) block are at risk because digoxin slows AV nodal conduction and can worsen bradyarrhythmias or progress to advanced heart block. In Wolff-Parkinson-White (WPW) syndrome, digoxin is especially hazardous, particularly when atrial fibrillation is present, because AV nodal blockade may promote preferential conduction down an accessory pathway and precipitate life-threatening ventricular tachyarrhythmias.[18] Structural cardiac conditions also matter; in restrictive cardiomyopathy, hemodynamics can be precarious, and digoxin may increase arrhythmic risk without clear symptomatic advantage. Finally, endocrine status influences pharmacokinetics: hypothyroidism delays digoxin

clearance, increasing the likelihood of elevated serum concentrations and toxicity, thereby necessitating conservative dosing and closer monitoring [18].

Monitoring

Monitoring is central to the safe and effective use of digoxin because the drug has a narrow therapeutic index and clinically meaningful variability in exposure across patients. Traditional references have described recommended serum digoxin levels ranging from approximately 0.8 to 2 ng/mL.[19] However, contemporary practice—especially in heart failure—has shifted toward lower target concentrations, reflecting evidence that higher levels correlate with increased adverse outcomes. Regardless of the specific target chosen, serum concentration should never be interpreted in isolation; it must be integrated with the patient's clinical status, renal function trajectory, electrolyte balance, ECG findings, and the presence of interacting medications. Accurate measurement begins with correct timing of blood sampling. Because digoxin undergoes a distribution phase after dosing, serum levels drawn too early can overestimate clinically relevant tissue exposure. For this reason, blood should be obtained at least 6 to 8 hours after the last dose to improve the accuracy and interpretability of the reported concentration.[19] The probability of toxicity rises as serum levels exceed 2.0 ng/mL, but it is equally important to recognize that toxicity may occur at lower levels in patients who are elderly, underweight, hypokalemic, hypomagnesemic, or experiencing renal impairment. As a practical safety measure, prescribers should recheck digoxin levels when there are significant medication changes—particularly additions of agents that alter absorption or clearance—and when clinical circumstances change, such as dehydration, acute kidney injury, or escalation of diuretic therapy that may precipitate electrolyte abnormalities [19].

Renal monitoring is especially critical because digoxin elimination is predominantly renal. Approximately 70% of digoxin is excreted by the kidneys, and clearance is closely proportional to glomerular filtration rate. Consequently, clinicians should request routine bloodwork to evaluate renal function and should interpret creatinine and estimated GFR trends rather than relying on a single value, particularly in older adults with low muscle mass. Close electrolyte surveillance is also mandatory. Potassium and magnesium disturbances increase myocardial sensitivity to digoxin and amplify arrhythmogenic potential, so periodic monitoring and proactive correction are key toxicity-prevention strategies.[20] Many clinical practices check digoxin levels about one week after initiation, since this allows concentrations to approach steady state in patients with normal renal function, and then reassess at regular intervals thereafter, with the frequency individualized to patient risk factors, stability of kidney function, and medication complexity.

Guideline recommendations refine how clinicians interpret "therapeutic" concentrations, especially for heart failure. The 2013 ACC Foundation guidance and the AHA recommend lower digoxin plasma concentrations—approximately 0.5 to 0.9 ng/mL—for heart failure, reflecting a benefit–risk balance that favors symptom control and reduced hospitalization while limiting toxicity. More recently, the 2022 AHA, ACC, and Heart Failure Society of America guidance suggests an upper limit of around 1.0 ng/mL and highlights that mortality risk increases at concentrations of 1.2 ng/mL or higher, supporting the use of low doses and conservative targets. In contrast, the therapeutic range for atrial fibrillation remains less definitively established, and recommendations vary from less than 0.9 up to 1.2 ng/mL. Some discussions propose targeting 0.5 to 1.0 ng/mL, emphasizing avoidance of supratherapeutic exposure rather than pursuit of higher levels for incremental rate control.[21] This lack of universal consensus reinforces the need for individualized monitoring strategies based on patient-specific risks and the clinical endpoint being pursued [21].

Electrocardiographic monitoring provides an additional layer of safety and can help differentiate expected pharmacologic effects from evolving toxicity. Digoxin commonly produces downsloping ST-segment depression, sometimes called the "reverse check" sign, where the ST segment appears characteristically "scooped," typically without ischemic Q-wave changes or pathologic T-wave inversions.[22] With regular digoxin exposure, clinicians may observe a shortened QT interval, prolongation of the PR interval, and T-wave flattening or inversion. While these findings can occur at therapeutic levels, progressive PR prolongation, marked bradycardia, new AV block, frequent ventricular ectopy, or atrial tachyarrhythmias in a patient receiving digoxin should prompt reassessment for toxicity, particularly when accompanied by gastrointestinal symptoms or visual disturbances. Routine ECGs are therefore valuable both at baseline and during follow-up, especially after dose changes or when interacting medications are introduced. In cases of overdose or life-threatening toxicity, digoxin immune fab is used as a specific antidote. This antibody fragment binds free digoxin, preventing it from attaching to its active sites and facilitating neutralization of toxic effects. However, careful monitoring is required after administration because reversal of digoxin's physiologic effects can lower serum potassium; clinicians must therefore monitor electrolytes closely and manage potassium shifts appropriately. Finally, broader outcome data underscore why rigorous monitoring matters. A systematic review reports an association between elevated serum digoxin concentrations and increased mortality and morbidity in patients with atrial fibrillation and heart failure with reduced ejection fraction, reinforcing the importance of careful dosing,

ongoing surveillance, and patient-specific therapeutic targets to optimize outcomes.[23]

Toxicity

Digoxin toxicity remains a clinically important problem because it can progress from nonspecific constitutional symptoms to malignant arrhythmias and hemodynamic collapse. The drug's narrow therapeutic index means that relatively small increases in exposure—whether from dosing errors, renal function decline, dehydration, electrolyte disturbances, or drug–drug interactions—can convert a therapeutic regimen into a toxic one. This risk is further amplified in older adults, patients with low lean body mass, and those with chronic kidney disease, because tissue distribution and clearance become less predictable. In addition, concerns have been raised about digoxin's association with increased mortality in certain populations, reinforcing the need for conservative dosing, careful monitoring, and early recognition of toxicity when it occurs. Overdose can be particularly dangerous because it may precipitate life-threatening arrhythmias and, in severe cases, malignant hyperkalemia.[22]

Signs and Symptoms of Overdose

The most frequently encountered manifestations of digoxin toxicity are gastrointestinal and constitutional complaints, including nausea, vomiting, anorexia, and fatigue.[22] These symptoms are clinically significant because they are common in many illnesses, leading to delayed recognition unless the clinician actively considers digoxin exposure as a cause. As toxicity worsens, cardiovascular and neurologic features become more prominent. Bradycardia is commonly observed, reflecting enhanced vagal tone and depressed conduction through the sinoatrial and atrioventricular nodes. Neurologic symptoms can occur as digoxin redistributes into the central nervous system; patients may report confusion and generalized weakness, and in chronic toxicity the spectrum may expand to lethargy, delirium, and profound debility. Visual changes are also characteristic and may include xanthopsia (yellow-tinged vision), diplopia, and photophobia.[24] These ocular complaints can be subtle and fluctuate, but when they occur in a patient taking digoxin—especially alongside gastrointestinal symptoms and bradycardia—they should raise strong suspicion for toxicity. Electrolyte abnormalities are central to both the development and interpretation of digoxin toxicity. Hyperkalemia is an especially important marker of acute, severe poisoning because it reflects extensive inhibition of the Na^+/K^+-ATPase pump and correlates with higher lethality risk.[22] Conversely, hypomagnesemia, and hypercalcemia increase myocardial sensitivity to digoxin and lower the threshold at which toxic effects appear. Loop diuretics frequently contribute to hypokalemia, thereby amplifying susceptibility even when serum digoxin levels are only modestly elevated. For this reason, toxicity can occur at lower serum

concentrations in the presence of potassium or magnesium depletion, and clinicians must interpret the digoxin level in the broader physiologic context rather than treating it as a standalone determinant [22].

Evaluation begins with a focused assessment of renal function and hemodynamic stability. Because renal clearance is the dominant elimination pathway for digoxin, changes in kidney function can rapidly shift a stable regimen toward accumulation. Practical evaluation includes blood urea nitrogen, serum creatinine, and careful monitoring of urine output, which can identify acute kidney injury or evolving renal hypoperfusion. Electrolytes—particularly potassium, magnesium, and calcium—should be measured promptly and corrected as clinically indicated. A 12-lead ECG is essential, as digoxin toxicity can produce a broad range of rhythm disturbances. Common findings include premature ventricular contractions, sinus bradycardia, atrial tachyarrhythmias with AV block, ventricular bigeminy, ventricular tachycardia, and ventricular fibrillation.[22] One rhythm disturbance is especially suggestive: bidirectional ventricular tachycardia, although rare, is classically associated with digoxin toxicity and is characterized by beat-to-beat alternation in the QRS axis.[25][26] Recognition of this pattern is clinically valuable because it can accelerate diagnosis in ambiguous presentations and prompt urgent antidotal therapy.

Management of Overdose

Management is driven by severity, rhythm instability, and electrolyte derangements, with the primary goals being stabilization, arrhythmia control, and reversal of digoxin's toxic effects. In patients with life-threatening hyperkalemia, urgent treatment is required; glucose and insulin are used to shift potassium intracellularly and reduce the immediate arrhythmic risk.[22] In acute overdoses, activated charcoal may be administered to reduce absorption and enhance elimination, with evidence suggesting it can shorten the effective elimination half-life of digoxin.[27] Because digoxin toxicity is often accompanied by bradyarrhythmias and ventricular ectopy, continuous cardiac monitoring is necessary, and antiarrhythmic therapy may be required when malignant ventricular rhythms occur. Lidocaine or phenytoin may be used for ventricular arrhythmias in the context of digoxin poisoning, particularly when ectopy or ventricular tachycardia threatens perfusion.[22] At the same time, clinicians must aggressively correct precipitating factors—especially hypokalemia and hypomagnesemia—while avoiding overcorrection that could produce iatrogenic complications. The definitive reversal agent for significant digoxin overdose is digoxin immune fab, an antibody fragment that binds free digoxin and prevents interaction with its pharmacologic target. In practice, its use is guided by clinical and laboratory severity markers. Indications include any life-threatening digoxin-related dysrhythmia, refractory hyperkalemia, a serum digoxin concentration greater than 15 ng/mL at any time or above 10 ng/mL when measured six hours after ingestion, acute ingestion of 10 mg in adults, acute ingestion of 4 mg in children, or chronic elevation of serum digoxin concentration accompanied by altered mental status, dysrhythmias, or severe gastrointestinal symptoms.[22] After immune fab administration, careful monitoring remains essential because reversal of digoxin's physiologic effects may change serum potassium dynamics, and arrhythmia patterns can evolve as bound digoxin is neutralized and redistributed. Overall, the management of digoxin toxicity requires rapid recognition, ECG-driven risk stratification, correction of electrolyte and renal contributors, and timely antidotal therapy when severe features are present.

Enhancing Healthcare Team Outcomes

Optimizing outcomes in patients receiving digoxin requires a deliberately coordinated interprofessional approach because the drug's narrow therapeutic index means that small deviations in dosing, renal clearance, electrolyte balance, or concomitant medications can precipitate clinically significant toxicity. Digoxin overdose is particularly dangerous, as it can trigger severe bradyarrhythmias, malignant ventricular dysrhythmias, and life-threatening hyperkalemia. These risks have fueled ongoing concern about a possible association between digoxin exposure and increased mortality in certain patient populations, prompting clinicians and researchers to emphasize conservative dosing, careful selection of candidates, and vigilant monitoring throughout therapy. In this context, high-quality digoxin management cannot be delivered by a single clinician working in isolation; it requires a team-based model in which responsibilities are shared, information is rapidly communicated, and care decisions are aligned across disciplines. Because digoxin therapy is strongly influenced by drug–drug interactions and comorbid conditions, frontline clinicians and advanced-practice providers play a central role in establishing appropriate indications, selecting conservative doses, and ensuring baseline evaluations are completed. Key initial tasks include verifying renal function, reviewing electrolyte status—especially potassium and magnesium—and confirming baseline cardiac rhythm and conduction via ECG. Throughout treatment, clinicians must interpret digoxin levels and clinical signs together, recognizing that toxicity can occur even at modest serum concentrations in high-risk individuals. When an acute presentation suggests toxicity, timely intervention is critical. Management frequently begins with supportive therapy, including intravenous hydration and electrolyte repletion, which can stabilize perfusion, correct precipitating abnormalities, and reduce arrhythmia risk.[28] However, supportive

therapy alone may be insufficient in severe cases, and delay in escalation may expose patients to substantial mortality risk [28].

Pharmacists are pivotal to both prevention and acute response. On the prevention side, pharmacists reconcile medications, identify interacting agents that elevate digoxin exposure or intensify AV nodal blockade, recommend dose adjustments for renal impairment, and advise on appropriate timing and interpretation of serum level monitoring. In suspected or confirmed toxicity, the pharmacist's role becomes even more time-sensitive. After assessment of serum digoxin concentrations and ECG findings, the clinician should promptly request digoxin immune fab through the pharmacy, because its availability, dosing, preparation, and administration logistics often depend on pharmacy coordination. Simultaneously, a structured medication-profile review should be undertaken to identify the cause of toxicity—such as recent initiation of a P-glycoprotein inhibitor or an agent that reduces renal clearance—so that the precipitating factor can be addressed and recurrence prevented. This workflow is most effective when pharmacists and prescribers communicate bidirectionally, ensuring that antidote ordering, electrolyte correction, and monitoring plans occur without gaps. Nursing staff are equally essential in optimizing outcomes because nurses are frequently the first to detect early warning signs of toxicity at the bedside. Continuous monitoring of vital signs and telemetry, early recognition of bradycardia, hypotension, altered mental status, nausea or vomiting, and prompt escalation to providers can determine whether deterioration is prevented or allowed to progress. Nursing care also includes strict intake and output measurement to support renal assessment, safe administration of IV fluids and electrolyte replacement, and meticulous documentation to support clinical decision-making. In intensive settings, nurses help implement post–immune fab monitoring, including serial electrolytes and ECG surveillance, given that reversal of digoxin effects can shift potassium dynamics and alter rhythm patterns. Specialist involvement should be targeted and proactive. Nephrology consultation may be appropriate if emergent renal support is required or if severe renal dysfunction complicates clearance and electrolyte management, even though digoxin itself is not effectively removed by conventional hemodialysis. Toxicology consultation can provide specialized guidance on complex cases, including mixed overdoses, atypical ECG manifestations, antidote dosing strategy, and nuanced electrolyte management. In situations where overdose is intentional, psychiatry involvement is crucial to evaluate self-harm risk, address underlying psychiatric illness, and coordinate safety planning and follow-up, thereby reducing the likelihood of recurrence and improving holistic outcomes. Finally, many patients with significant toxicity require admission to a monitored environment such as the medical intensive care unit or cardiac care unit under critical care supervision. In these units, interprofessional coordination becomes even more important: clinicians direct resuscitation and rhythm management, pharmacists ensure antidote and medication optimization, and nurses deliver continuous monitoring and rapid response. Clear handoffs shared situational awareness, and standardized protocols—covering when to check digoxin levels, when to administer immune fab, how to correct potassium and magnesium, and how to manage bradyarrhythmias—create reliable systems that minimize preventable harm. Through cohesive teamwork, rigorous monitoring, and rapid antidotal therapy when indicated, healthcare teams can reduce toxicity incidence, mitigate complications, and improve patient safety and outcomes related to digoxin therapy [28].

Conclusion:

Digoxin remains a clinically valuable but high-risk medication in modern cardiovascular care. While its ability to enhance myocardial contractility and control ventricular rate provides symptomatic benefit, its lack of mortality reduction and narrow therapeutic index limit its role to carefully selected patients. Current guidelines position digoxin as an adjunctive option for heart failure with reduced ejection fraction and for rate control in atrial fibrillation when beta blockers or calcium-channel blockers are contraindicated or ineffective. Safe use hinges on individualized dosing based on renal function, lean body mass, and comorbidities, with serum concentration targets generally between 0.5 and 0.9 ng/mL for heart failure. Vigilant monitoring of renal function and electrolytes is essential, as hypokalemia and hypomagnesemia markedly increase toxicity risk. Clinicians must remain alert to drug–drug interactions, particularly with P-glycoprotein inhibitors and AV nodal–blocking agents, which can precipitate bradyarrhythmias or elevate digoxin levels. Toxicity can present subtly with gastrointestinal or visual symptoms but may progress to malignant arrhythmias and hemodynamic collapse, requiring prompt recognition and antidotal therapy with digoxin immune fab. Ultimately, digoxin's continued use demands a multidisciplinary approach emphasizing conservative dosing, proactive monitoring, and patient education to optimize therapeutic benefit while minimizing harm.

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