GUIDED LECTURE NOTES
ADVANCED PHARMACOTHERAPEUTICS
HEART FAILURE

1. Heart Failure Pathophysiology
    a. Complex syndrome – structural or functional cardiac disorder that impairs the ability of the ventricles to fill or eject blood
    b. Cardiac output is insufficient to meet the metabolic demand of the body
    c. Determinates of Ventricular Function
        i. Preload, afterload
        ii. Contractility, stroke volume, CO
        iii. Heart rate
2. Types
    a. Left Ventricular Dysfunction
        i. Increase in end systolic volume
        ii. Increase in end diastolic volume
        iii. Pulmonary congestion
        iv. Decreased CO, hypoperfusion
    b. Compensatory Systems
        i. Sympathetic activation
        ii. Renin-angiotensin-aldosterone system

3. Classification of Heart Failure

American College of Cardiology Foundation/American Heart Association Heart Failure Classifications Stages A-D	New York Heart Association Heart Failure Classifications Stages I-IV	Treatment Options
Stage A – High risk for development of heart failure; no underlying structural cardiac disease (hypertension, diabetes mellitus, hyperlipidemia, etc.)	No Correlation	Lifestyle Modifications HTN –diuretics & ACEi ACEI – IF diabetes ARBS – IF ACEI intolerant patients
Stage B – Structural heart disease but asymptomatic	I. Patients with cardiac disease but no limitation of physical activity	ACEI in all patients, ARBs for those who are intolerant BB in most
Stage C – Structural heart disease with past or current symptoms of heart failure	II. Patients with slight, mild limitation of activity causes fatigue, palpitations, dyspnea or anginal pain, comfortable with rest and with mild exertion	ACEIs and BB in all patients Diuretics, digoxin Spironolactone
	III. Patients with marked limitations of activity, fatigue, palpitations, dyspnea or angina, comfortable only at rest	
Stage D – Refractory heart failure	IV. Symptoms even at rest	Inotropes- dobutamine Entresto (sacubitril/valsartan) VADs, transplantation, hospice

4. Common signs and symptoms
    a. SOB/ dyspnea/rales/orthopnea and paroxysmal nocturnal dyspnea/night cough
    b. JVD/ neck vein distention/hepatojugular reflux
    c. S3 gallop/cardiomegaly/ chest discomfort
    d. Nocturia/ankle edema
    e. fatigue, muscle weakness, or tiredness

Reduced EF HF (HFrEF)	Mid range HF (HFmrEF)	Preserved (HFpEF)
Heart failure with reduced ejection fraction symptoms and signs with LVEF <40%.	Heart failure with mid-range ejection fraction symptoms and signs with LVEF 40% to 49%. Other features include Increased natriuretic peptides BNP >35 picograms/mL Pro BNP >125 picograms/mL + least one additional criterion (a) relevant structural heart disease (b) diastolic dysfunction	Heart failure with preserved ejection fraction symptoms and signs with LVEF >50%. Other features include Increased natriuretic peptides BNP >35 picograms/mL Pro BNP >125 picograms/mL + least one additional criterion (a) relevant structural heart disease (b) diastolic dysfunction
Heart failure comprises a vast array of patient presentations from patients with normal left ventricular ejection fraction (LVEF) >50% to those with reduced myocardial contractility (LVEF <40%)		

5. Risk factors
    a. MI, dyslipidemia, HTN, LVH
    b. Exposure to cardiotoxic agents
    c. Drug abuse
    d. Valve disease/insufficiency
    e. Thyroid d/o
    f. FHX of heart failure
6. Pharmacological Management Heart Failure
    a. Loop Diuretics – Acute & chronic management; symptomatic heart failure = immediately decrease circulating volume
    b. ACEI – Chronic management of CHF = inhibiting sodium and water retention
    c. Beta Blockers – Chronic management = inhibit excess adrenergic stimulation
    d. Cardiac Glycosides – Chronic management = increase release of intracellular calcium
    e. Phosphodiesterase Inhibitors – Chronic Management = inhibits smooth muscle contraction
    f. Vasodilators – Acute and Chronic Management = vasodilation
    g. Dobutamine and Dopamine – Acute and Chronic management = beta1 and dopamine receptor agonists

Mineralocorticoid receptor antagonists	Diuretics	Beta blockers	CCB	ACEi/ARBS
Use if recent BNP>100 or ProBNP >360 (within 60 days) Carefully monitor K+ and renal function	Diuresis reduced pre-load- use with caution to prevent excessive diuresis and hypotension	Do not use unless coexistent angina symptoms	May be beneficial Evidence lacking	Use cautiously unless renal disease

7. Goals of treatment of chronic CHF

Goals of treatment of chronic CHF

Alleviate symptoms	Delay progression	Reduce mortality
Pharmacotherapeutics Lifestyle modifications to include dietary and nutritional modifications Exercise Health maintenance	control of BP in hypertensive patients weight loss in obese patients treatment of dyslipidemia in accordance with current guidelines optimization of glycemic control in patients with DM	Interventions proven to have beneficial impact on survival include: ACE inhibitors/ARBs Beta-blockers Aldosterone antagonists Nitrates Hydralazine cardiac resynchronization therapy implantable cardioverter-defibrillators
Prevention: health targets include hypertension, diabetes, dyslipidemia, obesity/metabolic syndrome and ischemic heart disease		

8. GOT FOR HFPEF (PRESERVED)
    a. HFpEF is largely governed by management of associated conditions and symptoms
    b. there is limited direct evidence to support a specific drug regimen
9. GENERAL PRINCIPLES FOR TREATMENT OF HFPEF:
    a. control of pulmonary congestion and peripheral edema with diuretics
    b. treatment of systolic hypertension
    c. prevention of rapid heart rates, particularly in patients with atrial fibrillation
    d. coronary revascularization in patients with coronary heart disease with ischemia judged to contribute to symptoms of HF
10. GOT FOR HFREF (REDUCED)
    a. improvement of symptoms and survival
    b. Attenuating/reversing the impact of adverse remodeling on the geometry and function of the left ventricle
11. INITIAL THERAPIES USED IN COMBINATION
    a. Diuretic
    b. Angiotensin system blocker
    c. angiotensin receptor-neprilysin inhibitor [ARNI], angiotensin converting enzyme inhibitor or angiotensin II receptor blocker
    d. Beta blocker
    e. Nitrates and hydralazine
        i. alternative to an angiotensin system blocker have demonstrated improved symptoms including reduction in hospitalization for HF and survival
12. TREATMENT CONSIDERATIONS
    a. Early therapy works best
    b. As heart failure progresses, non-selective beta blocker with both alpha and beta impact work better than Cardioselective types

c. The advent of neprilysin inhibitors (Entresto®)has dramatically decreased the risk of death and hospitalizations

13. HF MONITORING
    a. Functional capacity & Fluid status
        i. Weight changes _____
        ii. Jugular venous distension
    b. Cardiac rhythm
        i. _____
    c. Laboratory tests
        i. Electrolytes
        ii. Creatinine
        iii. Thyroid and liver function

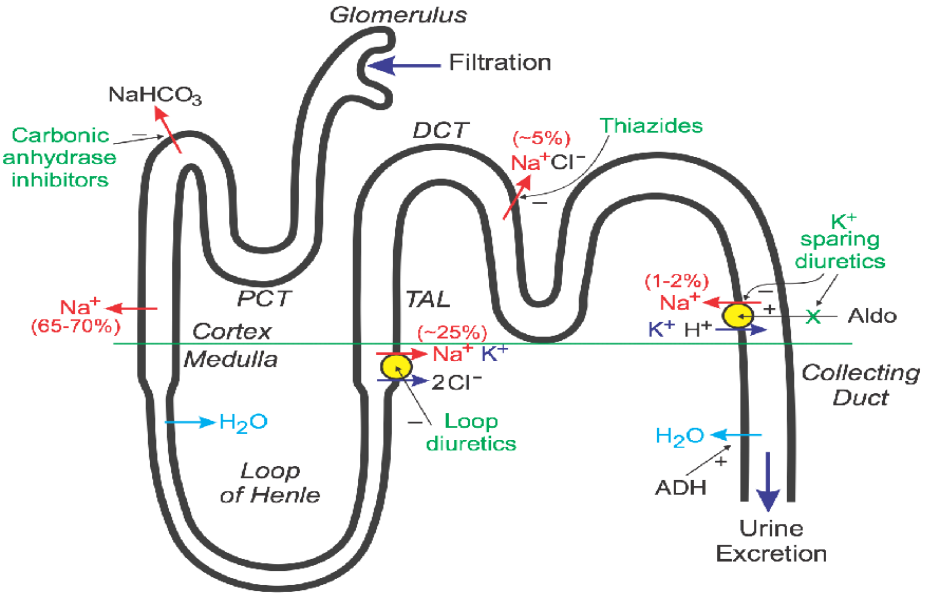
14. PATIENT VARIABLES AND HEART FAILURE
    a. Coronary artery disease
        i. Nitrites
        ii. Aspirin
    b. Chronic atrial fibrillation
        i. Warfarin or other new anticoagulants that reduce risk of stroke
    c. Diabetes
        i. ACEIs
        ii. Thiazides: may increase glucose levels
        iii. Beta blockers avoided
    d. Hypertension
        i. Use of diuretics early to decrease preload
        ii. ACEIs
    e. Hyperlipidemia
        i. Statin
    f. Infants and children
        i. Digoxin, thiazide, and loop diuretics all used
    g. Pregnancy
        i. ACEIs contraindicated in pregnancy
        ii. Diuretics may decrease placental perfusion

15. PATIENT EDUCATION
    a. treatment plan
        i. including pathophysiology and chronicity of heart failure
        ii. home monitoring _____
        iii. _____
    b. drug therapy
        i. patients should take exactly as directed
        ii. patient should not miss or double doses

MEDICATIONS CLASSES

16. Diuretics
    a. Thiazide diuretics
        i. HCTZ, chlorthalidone, indapamide, metolazone
        ii. High-dose therapy (HCTZ greater than 50) has increased risk of hypokalemia, increase in uric acid levels, and serious CV outcomes; use in combination vs pushing high doses
        iii. Watch with patients with hyperlipidemia

b. Potassium sparing:
    i. often used in combination with thiazide to reverse low potassium effect
        1. Triamterene
        2. Spironolactone
        3. Eplerenone (Inspra): next-generation aldosterone agent, Potassium sparing, selective aldosterone blocker



c. Diuretics ADRs: hypotension, decreased GFR, hypokalemia/hyperkalemia, electrolyte abnormalities, metabolic alkalosis, hyponatremia
    i. Major CYP3A4 substrate
    ii. Decreased effects with NSAIDs
    iii. Drug effects increase with grapefruit juice, azoles, CCBs
    iv. Increases effects of ACEI, ARB, BB, potassium replacement
    v. Cost: approximately $110 to $125/month without superior outcomes
d. Monitoring
    i. BP, HR, edema, weight gain, dyspnea, cough, urine output
    ii. Prior to initiating therapy
        1. BUN, creatinine, electrolytes (sodium, potassium, calcium, and magnesium), uric acid, and glucose levels
    iii. Ongoing monitoring of electrolytes
e. Patient education
    i. Take as directed early in day if there are urination issues.
    ii. Do not skip or double dose.
    iii. Monitor weight.
    iv. Must drink fluids!!

17. Loop diuretics Class information
    a. Meds: Furosemide (Lasix); Bumetanide (Bumex); Torsemide
    b. lowest dose should be titrated upward until a therapeutic effect is achieved or an adverse effect limits further titration
    c. In patients with persistent signs of fluid overload, diuretics may be necessary.
    d. LOOP Action : Inhibit chloride and NA++ reabsorption in the Loop of Henle, proximal and distal tubules

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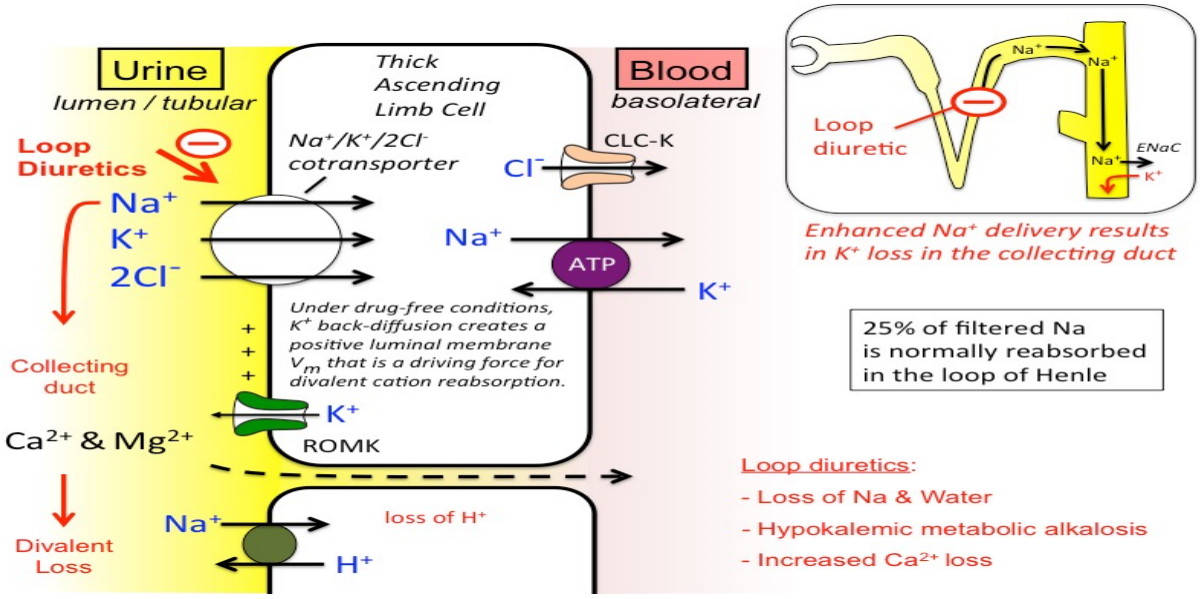

19. Ace Inhibitors in heart failure treatment
    a. *****ACEi have shown to decrease the morbidity and mortality associated with heart failure****
    b. Mechanism of Action
    inhibits angiotensin converting enzyme, interfering w/ conversion of angiotensin I to angiotensin II
    c. Reduction in GFR (as much as 30% (severe) but usually 5-25%; careful use in patients with renal artery stenosis, PCKD, nephrosclerosis

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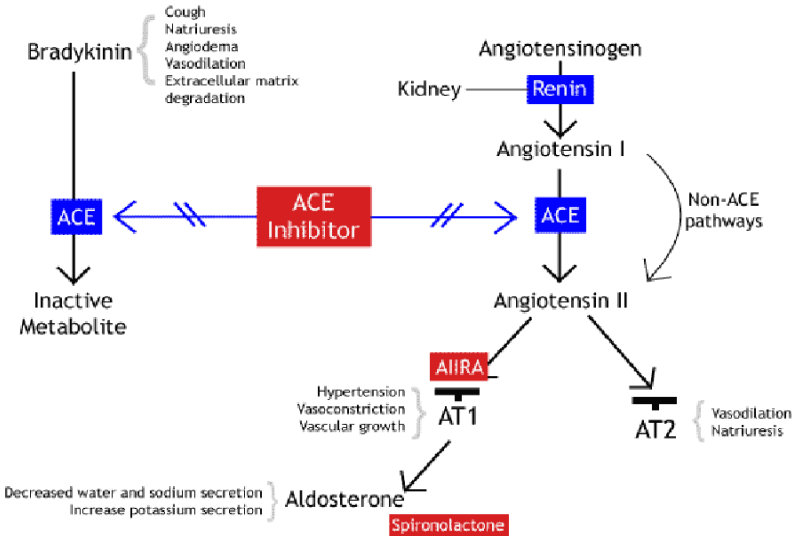


   iv. ******ACEi have shown to decrease the morbidity and mortality associated with heart failure****

e. ACEIs Pharmacodynamics
   i. Inhibition of angiotensin-converting enzyme (ACE) activity results in decreased production of both angiotensin II (AT II) and aldosterone
   ii. Can lower vascular resistance without decreasing cardiac output (CO) or glomerular filtration rate (GFR)
   iii. Does not produce reflex tachycardia
   iv. Strong evidence for CV and cerebrovascular risk reduction, HF, and slowing renal disease
   v. Improves oxygenation to heart muscle, decreases inappropriate remodeling of heart muscle after myocardial infarction (MI) or with heart failure, reduces effects of diabetes on the kidneys
   vi. Improves insulin sensitivity, does not affect glucose metabolism, or raise serum lipid levels

Common ACEIs

Drug	Initial Dose	Maximum Dose
Benazopril	5 mg if on diuretic; 10 mg if not on diuretic	80 mg/day
Captopril	25 mg 2 to 3 times per day	450 mg/day
Enalapril	2.5 mg twice daily if on diuretic; 5 mg twice daily if not on diuretic	40 mg/day
Fosinopril	10 mg daily	80 mg/day
Lisinopril	10 mg daily	80 mg/day
Moexipril	7.5 mg prior to meal once/day	60 mg/day

f. ACEIs Use
   i. Younger Caucasian patients
      1. Patients with angina prevents formation of AT II and decreases pulmonary vascular resistance by decreasing retention of sodium and water and reducing extracellular fluid and preload
      2. Patients with diabetes prevents or slows nephropathy
      3. After MI and HF, for ventricular remodeling
   ii. Not as effective in African American patients
      1. When combined with a diuretic, race no longer an issue
      2. However, three to four times greater risk of angioedema in African Americans and Asians

g. ACEIs Monitoring
    i. Possible orthostasis within 1 hour of administration when starting and with each dosage change
h. Patient education
    i. Do not double dose if one is missed
    ii. Hypotension most common ADR
    iii. Cough common with older-generation agents
i. Adverse drug reactions (ADRs):
    i. dry cough (bradykinin- mediated)
    ii. hypotension, loss of taste
    iii. angioedema, blood dyscrasias
    iv. teratogenicity, hyperkalemia
    v. acute renal failure
    vi. cholestatic jaundice, pancreatitis, rash

20. Angiotensin II Receptor Blockers
    a. Prevent binding of AT II to receptors in kidney, brain, heart, and arterial walls
    b. Inhibit the renin-angiotensin-aldosterone system (RAAS) and cause fall in peripheral resistance
    c. Evidence supports use in kidney disease until late stage and heart failure, but not all forms are renal protective like ACEI
    d. No bradykinin-mediated cough like ACEI
    e. Considered alternatives for patients who cannot tolerate ACE or become resistant
    f. Many combined with hydrochlorothiazide (HCTZ)
    g. ARB CYP450 Example
        i. Pharmacokinetics (Losartan)
        ii. CYP2C9
            1. Extensive first-pass metabolism resulting in 33% bioavailability
            2. Inducers: rifampin, barbiturates
            3. Inhibitors: lovastatin, sulfamethoxazole, and trimethoprim (SMZ/TMP), fluconazole, Fluvastatin, fluvoxamine, sertraline
        iii. ADRs: similar to ACEIs
            1. Typically no problem with cough
        iv. Monitoring
            1. Like ACEI orthostasis with dose changes
        v. Patient education
            1. Do not double dose if one is missed
            2. Hypotension most common ADR

Angiotensin II Receptor Blockers

Drug	Initial Dose	Maximum Dose
Candesartan	40 mg daily	80 mg/day
Esprosartan	600 mg daily	800 mg/day
Irbesartan	150 mg daily	300 mg/day
Losartan	50 mg daily	100 mg/day
Olmesartan	20 mg daily	40 mg/day
Telmisartan	40 mg daily	80 mg/day
Valsartan	80 mg daily	320 mg/day

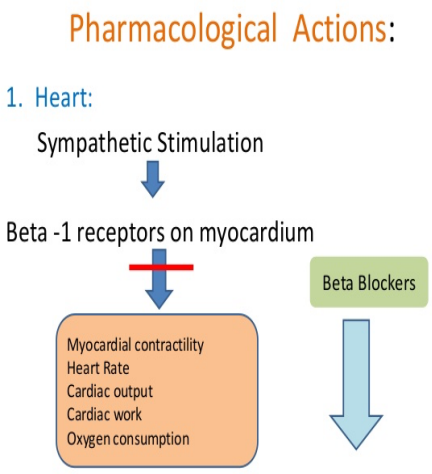
21. New Drug Class: Neprilysin Inhibitors
    a. Sacubitril/valsartan (Entresto) decreases hospitalizations and death in chronic HF
    b. Ejection fraction (EF) < 40%
    c. Taken in place of ACE or ARB
    d. Not given with BBs, such as carvedilol
    e. increases renal blood flow and improves diuresis
    f. Require 36-hour washout between ACE/ARB/BB

g. Sometimes called “game changer medication”

22. Direct Renin Inhibitors Alsikiren (Tekturna)
    a. Also works on the RAAS
    b. Can be used for HTN, awaiting word on HF; not same MI indication as ACEI and ARB
    c. Does not have the same renal protective properties as ACEI
    d. For example, ACEI must stop when creatinine rises
    e. Same issues in pregnancy, perhaps fewer issues with potassium (K+) and cough

23. Adrenergic Antagonists- Beta Blockers
    a. Beta blockers
        i. Action: antagonize or block the effects of catecholamines
        ii. Can be “selective” to beta1 receptors or “nonselective” to beta1 receptors
        iii. Mainly used for HTN and after myocardial infarction (MI)
    b. Selective vs nonselective beta blockers
        i. Propranolol vs atenolol
    c. Clinical use
        i. Angina, HTN, Heart failure, post-MI, anti-dysrhythmia
        ii. Migraine prophylaxis
    d. Beta Blockers in heart failure
        i. renin release from the glomerulus = less outflow from kidneys and less water retention
        ii. heart failure mechanism is aimed at reducing the effect of sympathetic stimulation
        iii. reducing heart rates, myocardial energy demands, remodeling, arrythmia promotion, and RAA system

    e. Beta Adrenergic Blockers
        i. First Generation (non-selective) – Propranolol (Inderal); Nadolol (Coradard); Carvedilol (Coreg)
        ii. Second Generation (Beta 1 Receptor selective) – Atenolol (Tenormin); Penbutolol (Levatol); Metoprolol (Lopressor)
        iii. Third Generation (Beta and Alpha Receptor selective) – Nebivolol (Bystolic)



    f. Beta blocker MOA in heart failure
        i. renin release from the glomerulus = less outflow from kidneys and less water retention
        ii. heart failure mechanism is aimed at reducing the effect of sympathetic stimulation
        iii. reducing heart rates, myocardial energy demands, remodeling, arrythmia promotion, and RAA system
        iv. Action: antagonize or block the effects of catecholamines
            1. Can be “selective” to beta1 receptors or “nonselective” to beta1 receptors
            2. Mainly used for HTN and after myocardial infarction (MI)

24. CARDIAC GLYCOSIDE: Digoxin
    a. Digoxin: highly selective inhibitor of the adenosine triphosphatase (ATPase) system
    b. Inhibition of this pump results in sodium and calcium buildup inside the cell, which leads to increased contractility of heart muscle.
    c. basis for its use in two clinical situations

i. heart failure due to systolic dysfunction
ii. certain supraventricular tachyarrhythmias

d. One meta-analysis suggests that digoxin use in patients with heart failure is associated with a higher risk of all-cause mortality
e. reduces the composite end point of mortality or hospitalizations but does not reduce all-cause mortality.
f. Dosing
    i. Low doses
        1. 0.125 mg/day or every other day should be used initially if the patient is:
        2. over 70 years old
            a. has impaired renal function
            b. has a low lean body mass
    ii. Higher doses
        1. 0.375 to 0.5 mg/day are rarely used or needed
        2. Digoxin should be used cautiously with plasma level monitoring
g. ADRs
    i. Gastrointestinal (GI) most common: anorexia, nausea/vomiting, diarrhea
    ii. Central nervous system: fatigue, disorientation, depression, hallucinations, visual disturbances – yellow vision and green halos around lights
    iii. Cardiac: bradycardia, premature ventricular contractions, junctional and atrioventricular (AV) block arrhythmias, and bigeminy
    iv. Avoid using in patients with normal left ventricular systolic function
h. Toxicity: atrial arrhythmias/tachycardia in children
    i. Serum concentrations greater than 1 mg/mL increase mortality.
    ii. Initiate therapy at the lowest dose possible.
    iii. Well absorbed orally
i. PK/PD
    i. NOT extensively metabolized, excreted unchanged by kidneys
    ii. Half-life is 36 to 48 hours
    iii. In the absence of oral or intravenous loading, steady state is achieved in four half-lives or 1 week
    iv. Reduced clearance of digoxin with drug interaction
        1. Quinidine, amiodarone, verapamil, diltiazem
j. Monitoring
    i. Diagnosis of toxicity is based on both clinical and laboratory data.
    ii. Toxicity commonly occurs with serum levels greater than 2 ng/mL.
    iii. Monitor potassium levels.
k. Patient education
    i. Take at same time each day.
    ii. Do not double doses.
    iii. Monitor for signs of toxicity.
    iv. Take pulse hold for heart rate (HR) less than 60 or greater than 100 beats per minute.
l. Baseline Parameters:
    i. Cr, electrolytes, HR at baseline, then periodically
    ii. serum drug levels
m. Metabolism: liver 16% and CYP450: unknown
n. Excretion: urine (mainly unchanged) Half-life: 1.5-2 days and 3.5-5 days if anuric