

## Considerations for Safe Medication Use in Chronic Kidney Disease

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### Objectives

- Discuss chronic kidney disease
- Identify concerns surrounding safe medication use in chronic kidney disease
- Choose appropriate medications for use in chronic kidney disease

## Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation.
- This discussion will include the use of medications for off-label indications.

## Chronic Kidney Disease & End Stage Renal Disease Overview

## Kidney Functions

- What do the kidneys do for us?
  - Regulate fluid balance
  - Regulate electrolyte balance
  - Release hormones
  - Control red blood cell production
  - Filter blood
    - Remove waste
    - Remove drugs



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## Chronic Kidney Disease (CKD)

- Definition
  - Progressive kidney damage, present for  $\geq 3$  months
  - GFR  $< 60$  mL/min/1.73m<sup>2</sup> for  $\geq 3$  months
- Causes
  - #1 in U.S. = diabetes and uncontrolled hypertension
  - Vascular disease, glomerular disease, polycystic kidney disease, recurrent stones or obstruction, birth defects
  - Drugs and toxins (NSAIDs, IV contrast)
- Risk factors
  - Age, diabetes, HTN, hyperlipidemia, smoking, autoimmune diseases, genetics

## CKD Staging

- National Kidney Foundation K/DOQI:

Stage	GFR (mL/min/1.73m <sup>2</sup> )	Description
1	≥ 90	Kidney damage with normal or increased GFR
2	60-89	Kidney damage with mildly decreased GFR
3	30-59	Moderately decreased GFR
4	15-29	Severely decreased GFR
5	<15 or on dialysis	End stage renal disease (ESRD)

K/DOQI = Kidney Disease Outcomes Quality Initiative

## End Stage Renal Disease (ESRD)

- Stage 5 renal failure
  - With or without renal replacement therapy (dialysis)
- Complications
  - Anemia
  - Cardiovascular disease
  - Secondary hyperparathyroidism
  - Osteoporosis
  - Fluid and electrolyte imbalance

## Common ESRD Symptoms

- Weakness, fatigue, malaise
- Intractable nausea/vomiting
- Itching
- Leg cramps
- Edema
- Taste abnormalities
- Shortness of breath
- Bleeding abnormalities
- Pain

## Pharmacokinetics in CKD

- Absorption
- Distribution
- Metabolism
- Elimination
  - Removal of medication from the body
  - Most altered in renal disease

## Pharmacokinetics in CKD

- Glomerular filtration rate (GFR)
  - Measures how well the kidneys are functioning to filter out drugs and toxins
  - As GFR slows down with advanced renal disease, drugs are not eliminated from the body as quickly



## Take Note...



- GFR declines by approximately 8 ml/min every decade of life after age 40
- A healthy adult at age 70 has GFR 70 ml/min

## Effect on Medications

- Prolonged drug effects
- Slower drug elimination
- Increased serum drug levels
- Increased risk of side effects and toxicity

## Barriers to Appropriate Medication Use

- Increasing elderly population and polypharmacy
- Increased risk of toxicity and adverse drug reactions
- Clinician unfamiliarity with proper dosing
- Patient fear of medication use due to adverse effects

## Recognizing Adverse Drug Reactions

- Side Effect
  - Unintended but known/anticipated effect; may be favorable
  - Occurs when drug is used correctly and in therapeutic range
  - Reversible when drug removed; sometimes develop tolerance
- Adverse Drug Reaction (ADR)
  - Noxious and unintended effect from a drug
  - Occurs at doses normally used for proper disease treatment
  - Incidence and severity varies by patient characteristics and drug-related factors
  - \*Toxicity can be considered an ADR
    - Elevated blood levels or enhanced drug effects that occur during appropriate use

## Recognizing Adverse Drug Reactions

- Drugs most frequently involved in ADRs
  - Cardiovascular agents
  - Antibiotics
  - Diuretics
  - NSAIDs
  - Anticoagulants
  - Anti-diabetics
- Risk factors for ADRs
  - Decreased GFR / kidney disease
  - Multiple comorbid conditions
  - Liver disease
  - Polypharmacy



## Typical Symptoms of ADRs

### In adults & elderly

- diarrhea
- nausea
- loss of appetite
- electrolyte imbalance
- renal impairment
- bleeding

### Specific to the elderly

- delirium
- constipation
- orthostatic hypotension
- falls

\*Rule of thumb in geriatric medicine:  
Assume every change in status was caused by a medication

## Considerations for Medications for Comorbid Disease States

Common Offenders and Safer Alternatives

## Case: Mrs. Dalton

- 78 y/o female living at home with daughter & son-in-law
- PMH: CVA, CAD, A-fib, DM Type 2, CKD stage IV
  - Recent fall with hip fracture and repair, ECF placement x2 months for rehab, remained bedbound, developed Stage III pressure ulcer
- SH: widowed x5 years
- BP 115/82 HR 91 CrCL = 25ml/min

Patient did not rehab well and disliked living at the ECF. Family upset that she developed the pressure ulcer and decided to bring her home. Home health RN visits every other day to provide wound care.

## Mrs. Dalton - Medications

Rivaroxaban (Xarelto®) 20mg PO daily  
 Lisinopril (Zestril®) 5mg PO daily  
 Diltiazem (Cardizem®) CD 120mg PO daily  
 Digoxin (Lanoxin®) 125mcg PO daily  
 Glipizide (Glucotrol®) 10mg PO twice a day  
 Sitagliptin (Januvia®) 50mg PO daily  
 Ranitidine (Zantac®) 150mg PO twice a day  
 Calcium citrate 950mg PO daily  
 Vitamin D 400 IU PO daily  
 Polyethylene glycol (Miralax®) 17g in 8 oz. water PO daily  
 Hydrocodone/APAP (Norco®) 5/325mg PO q4h PRN pain  
 Acetaminophen (Tylenol®) 500mg PO q4h PRN pain

## Case: Mrs. Dalton

- During visit for wound care, RN notices the patient is confused and not acting like herself
  - Family also notices the confusion and thinks their mom is having trouble seeing correctly. They ask RN what could be causing these new symptoms.

Could medications be causing the symptoms?

## Medications for Common Disease States

- Certain medications for the following conditions should be used cautiously in CKD:
  - Cardiac disease
  - Diabetes
  - GI conditions
  - Infections
- Doses may need to be adjusted based on CrCL

## Cardiac Medications

- Anticoagulants
  - Drugs to avoid or make dose adjustments based on CrCL
    - Rivaroxaban (Xarelto®), dabigatran (Pradaxa®), apixaban (Eliquis®), enoxaparin (Lovenox®)
      - Increased serum levels = increased bleeding risk
      - Caveat: no monitoring necessary for these medications
  - Alternative
    - Warfarin (Coumadin®) – anticoagulant of choice in severe or end stage renal disease
      - Regular INR monitoring necessary to avoid adverse effects

## Cardiac Medications

- ACE-Inhibitors
  - Lisinopril (Zestril®), enalapril (Vasotec®), benazepril (Lotensin®)
    - Adjust dose or d/c in ESRD due to risk of worsening renal function
- Cardiac glycoside
  - Digoxin (Lanoxin®)
    - Reduce dose in CKD and ESRD to avoid adverse effects of nausea, dizziness, vision changes, mental status changes
    - Monitor serum level and adjust to safe therapeutic dose
    - *\*Clinical pearl: Patients are at higher risk of digoxin toxicity with concomitant use of loop diuretics*

## Mrs. Dalton - Medications

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 Lisinopril (Zestril®) 5mg PO daily  
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## Diabetes Medications

- **Sulfonylureas**
  - Glyburide (Diabeta®), glipizide (Glucotrol®), glimepiride (Amaryl®)
    - Use caution in advanced renal disease due to decreased clearance and high risk of hypoglycemia
    - Manufacturer recommends adjusting doses based on CrCL for glipizide and glimepiride
      - Use conservative initial and maintenance glyburide doses
    - Monitoring: fasting blood sugar and symptoms of hypoglycemia
- **Insulin**
  - Clearance decreased in CKD, monitor blood sugar closely

## Diabetes Medications

- Metformin (Glucophage®)
  - Do not use if serum creatinine >1.5mg/dl in male or >1.4mg/dl in female
    - Increased risk of lactic acidosis – **boxed warning**
    - May present as abdominal distress, malaise, myalgia, respiratory distress, somnolence
- DPP-IV Inhibitors
  - Sitagliptin (Januvia®), saxagliptin (Onglyza®), alogliptin (Nesina®)
    - Adjust dose based on CrCL– lower the dose in advanced CKD
    - Use lower doses of insulin and sulfonylureas with this drug class

## Mrs. Dalton - Medications

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## Acid Suppression Medications

- Histamine-2 blockers
  - Ranitidine (Zantac®), famotidine (Pepcid®), cimetidine (Tagamet®), nizatidine (Axid®)
    - All require dose reduction based on CrCL
    - Risk of adverse effects in renal disease, especially CNS effects
- Alternative
  - Proton Pump Inhibitors (PPIs)
    - Ex: omeprazole (Prilosec®), lansoprazole (Prevacid®)
    - No dose adjustment necessary in renal disease

## Gastrointestinal Medications

- Magnesium-containing medications
  - Magnesium hydroxide (Milk of Magnesia®) for constipation
  - Aluminum/magnesium/simethicone (Maalox®, Mylanta®) for stomach acid relief
    - Both magnesium and aluminum can accumulate in renal disease
    - Use not recommended in ESRD
    - Magnesium may cause diarrhea and GI cramping
    - Aluminum accumulation can cause constipation and GI cramping

## Mrs. Dalton - Medications

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## Case: Mrs. Dalton

- Medications that may be causing current symptoms
  - Cardiac medications: digoxin
    - Draw serum level – if high, dose every other day and re-check
  - Diabetes medications: glipizide
    - Check blood sugar – if low, decrease dose or discontinue
  - Antacid: ranitidine
    - Decrease dose to reduce risk of CNS effects
- Medications requiring dose adjustment per CrCL
  - Cardiac medications: rivaroxaban
    - Reduce dose to 15mg daily to reduce bleed risk



## Case: Mrs. Dalton

- MD adjusted medication doses
  - Digoxin serum level was high, now taking 125mcg QOD
  - FBS running 70-80mg/dL, glipizide dose reduced to 5mg PO BID
  - Decreased rivaroxaban dose to 15mg daily
  - Decreased ranitidine dose to 150mg PO daily
- Mental status improved, confusion resolved
- Now Mrs. Dalton has a UTI
  - Catheter was inserted 1 month ago
  - MD ordered ciprofloxacin 500mg PO q12h x10 days
  - Is this dose appropriate for her renal function?

## Anti-Infective Medications

- Common oral anti-infectives that require dose adjustments in renal disease
  - Antibiotics
    - Penicillins: amoxicillin (Amoxil®), amoxicillin/clavulanate (Augmentin®)
    - Cephalosporins: cephalexin (Keflex®), cefdinir (Omnicef®)
    - Fluoroquinolones: ciprofloxacin (Cipro®), levofloxacin (Levaquin®)
    - Other: sulfamethoxazole/trimethoprim (Bactrim®)
    - *Note: nitrofurantoin (Macrobid®) ineffective in mild CKD*
  - Antifungals & Antivirals
    - Azole antifungals: fluconazole (Diflucan®)
    - Antivirals: acyclovir (Zoviraxv), valacyclovir (Valtrex®)

## Anti-Infective Medications

- Neglecting to adjust dose leads to increased side effect risk
  - Often GI-related effects
- Alternative oral anti-infectives that do not require dose adjustment in renal disease
  - Antibiotics
    - Fluoroquinolones: moxifloxacin (Avelox®)
    - Macrolides: azithromycin (Zithromax®)
    - Tetracyclines: doxycycline (Vibramycin®)

## Take Note...



- Medications that are properly adjusted based on CrCL can be used safely in renal disease
- It is not necessary to use an alternative that doesn't require dose adjustment for CrCL

## Case: Mrs. Dalton

- Ciprofloxacin dose should be adjusted for her renal impairment
  - MD ordered ciprofloxacin 500mg PO q12h x10 days
    - This order is appropriate for a complicated UTI with normal renal function
  - Dose adjust for CrCL 15-29 ml/min: 250-500mg PO q18h

Recommendation: ciprofloxacin 250mg PO q12h x10 days

## Considerations for Medications for Common Symptoms in ESRD

Common Offenders and Safer Alternatives

## Common ESRD Symptoms

- Weakness, fatigue, malaise
- Intractable nausea/vomiting
- Itching
- Leg cramps
- Edema
- Taste abnormalities
- Shortness of breath
- Bleeding abnormalities
- Pain

## Case: Mr. Bernard

- 72 y/o male admitted to hospice for ESRD
- PMH: hemodialysis x2 years (stopped 3 days ago), DM type 2, dementia, GERD, peripheral neuropathy, anemia
- PPS 30% FAST 6a
- BP 110/70 HR 79 CrCL < 10ml/min
- Bedbound, normal swallowing, lives at home w/ wife
- Complains of nausea (new), pain, and fatigue

## Mr. Bernard - Medications

Aspirin 81mg PO daily  
Donepezil (Aricept®) 10mg PO HS  
Omeprazole (Prilosec®) 20mg PO daily  
Insulin glargine (Lantus®) 10 units subQ HS  
Gabapentin (Neurontin®) 600mg PO BID  
Ferrous sulfate 325mg PO BID  
Vitamin C 250mg PO daily  
Simvastatin (Zocor®) 20mg PO HS  
Senna/docusate (Senna-S®) 8.6/50mg PO BID  
Hydrocodone/APAP (Norco®) 5/325mg PO QID  
Tramadol (Ultram®) 50mg 1-2 tablets PO q6h PRN pain

## Case: Mr. Bernard

- Hospice RN would like to order a comfort care kit containing the following standard orders:
  - Morphine 20mg/ml solution, 5mg PO/SL q1h PRN pain or dyspnea
  - Haloperidol 0.5mg PO/SL/PR q4h PRN nausea/vomiting or agitation
  - Lorazepam 0.5mg PO/SL q4h PRN anxiety or dyspnea
  - Atropine 1% ophth. sol. 2-4 drops SL q4h PRN secretions
  - Acetaminophen 650mg rectal suppository q4h PRN fever
- How should we address Mr. Bernard's current symptoms?
- Should any current or CCK medication doses be adjusted?

## Pain

- Causes are commonly multi-factoral
  - Painful syndromes related to ESRD
    - Calciphylaxis, nephrogenic fibrosis, renal osteodystrophy
  - Dialysis pain
    - Needle insertion
    - Muscle cramps & headaches during the procedure
- Comorbid disease states associated with pain
  - Osteoarthritis
  - Diabetic neuropathy
  - Peripheral vascular disease

## Pain Meds in Advanced CKD and ESRD

Safest for Use	
Methadone	Fentanyl
Acetaminophen	
Use Cautiously or Adjust Dose	
Morphine	Oxycodone
Hydrocodone	Hydromorphone
Tramadol	TCAs
Gabapentin	Pregabalin
AVOID Use	
Codeine	Meperidine
NSAIDS	Tapentadol

## Pain Medications

- Acetaminophen (Tylenol®)
  - Generally considered safe and first-line for mild to moderate pain in renal failure
  - No dose adjustment necessary – limit to 4 g per day
- NSAIDs
  - Ex: ibuprofen (Motrin®), naproxen (Naprosyn®), meloxicam (Mobic®), celecoxib (Celebrex®)
  - Use in renal failure carries several risks:
    - May further deteriorate kidney function or cause irreversible damage
    - Increased risk of bleeding
  - *Avoid use in advanced CKD and ESRD*

## Pain Medications

- Tramadol (Ultram®)
  - Parent drug and metabolite excreted renally
  - Use low doses and longer dosage interval
  - GFR < 30 ml/min: 50-100mg every 12 hours
- Tapentadol (Nucynta®)
  - Renally excreted, mostly inactive metabolites
  - No dosage adjustment necessary GFR ≥ 30 ml/min
  - Not studied in GFR < 30 ml/min – *avoid use*

## Pain Medications

- Opioids
  - Most are eliminated via the kidneys
  - Accumulation of metabolites can cause adverse effects and toxicity
  - Prolonged effect, half life significantly lengthened for most
  - Some opioids removed through dialysis
  - Some opioids are safer than others
  - In general, use lower starting doses and longer dosage intervals

## Morphine

- Morphine Pharmacokinetics
  - Metabolites M6G and M3G renally eliminated
  - Elimination slower in ESRD → accumulation
  - M6G has more potent analgesic effects than morphine; may cause sedation and respiratory depression
  - M3G may cause CNS excitation manifesting as hyperalgesia, myoclonus, seizures (**neurotoxicity**)
    - Risk increases as dose and dosing frequency increases
  - *Use with caution in CKD and avoid prolonged use in ESRD*



## Take Note...



- Morphine use is NOT contraindicated in ESRD
- May be used safely with caution
- Low starting doses
- Longer dosage intervals

## Pain Medications

- Opioids to avoid
  - Codeine
    - Metabolite accumulation can lead to serious effects such as sedation, respiratory depression and hypotension
  - Meperidine (Demerol®)
    - Accumulation of normeperidine metabolite causes side effects of tremors, myoclonus, seizures and delirium
- Opioids to use with caution
  - Oxycodone (Roxicodone®, OxyContin®), hydromorphone (Dilaudid®), hydrocodone (Norco®), morphine (MS Contin®)
    - Use lower starting dose and/or lengthen dosing interval

## Pain Medications

- Opioids safest for use
  - Methadone (Dolophine®)
    - Excreted mostly in feces; favorable option for nociceptive *and* neuropathic pain control in ESRD
    - *Due to unique pharmacokinetics, consult a pain management specialist for dosing*
  - Fentanyl (Duragesic®)
    - Inactive metabolites primarily renally excreted
    - Appears safe for use
    - *Do not use fentanyl transdermal patches on opioid-naïve patients*

## Pain Medications

- Tricyclic antidepressants (TCAs)
  - Ex: amitriptyline (Elavil®), nortriptyline (Pamelor®)
  - No recommended dosage adjustments in renal failure
  - Use with caution due to anticholinergic side effects
    - Dry mouth, tachycardia, constipation, confusion, urinary retention
- Anticonvulsants
  - Gabapentin (Neurontin®) and pregabalin (Lyrica®)
  - Require dose adjustment in renal disease
    - Dosing recommended according to estimated GFR
    - Initiate with low dose & monitor for sedation, dizziness, fatigue, tremor

## Mr. Bernard - Medications

Aspirin 81mg PO daily  
Donepezil (Aricept®) 10mg PO HS  
Omeprazole (Prilosec®) 20mg PO daily  
Insulin glargine (Lantus®) 10 units subQ HS  
Gabapentin (Neurontin®) 600mg PO BID  
Ferrous sulfate 325mg PO BID  
Vitamin C 250mg PO daily  
Simvastatin (Zocor®) 20mg PO HS  
Senna/docusate (Senna-S®) 8.6/50mg PO BID  
Hydrocodone/APAP (Norco®) 5/325mg PO QID  
Tramadol (Ultram®) 50mg 1-2 tablets PO q6h PRN pain

## Case: Mr. Bernard

### Comfort kit medications to add:

- Morphine 20mg/ml solution, 5mg PO/SL q1h PRN pain or dyspnea
- Haloperidol 0.5mg PO/SL/PR q4h PRN nausea/vomiting or agitation
- Lorazepam 0.5mg PO/SL q4h PRN anxiety or dyspnea
- Atropine 1% ophth. sol. 2-4 drops SL q4h PRN secretions
- Acetaminophen 650mg rectal suppository q4h PRN fever

## Edema

- Causes
  - Sodium retention, volume expansion
- Treatment
  - Sodium-restricted diet
  - Loop diuretic ± thiazide diuretic
- Diuretic therapy
  - Not recommended if anuric (<100ml/day)
  - Monitor blood pressure, hydration status, urine output, serum electrolytes

## Edema - Diuretics

- Preferred agents
  - Loop diuretics: furosemide (Lasix®), torsemide (Demadex®), bumetanide (Bumex®)
    - Higher doses may be needed for response in CKD and ESRD
  - Thiazide diuretics: hydrochlorothiazide (Microzide®), metolazone (Zaroxolyn®)
    - Ineffective in CrCL < 30ml/min unless used with a loop diuretic
- Avoid potassium-sparing diuretics
  - Spironolactone (Aldactone®), triamterene (Dyrenium®)
    - HyperK+ risk; adjust dose in CKD and avoid use if CrCL < 30ml/min

## Nausea

- Causes
  - Uremia
  - Fluid/electrolyte imbalance
  - Medication-induced
  - Gastroparesis
- Treatment based on etiology
  - Target chemoreceptor zone
  - Discontinue offending medication
  - Increase gastric motility

## Nausea – Antiemetics

- Chemoreceptor trigger zone targeting agents
  - Haloperidol (Haldol®), prochlorperazine (Compazine®), promethazine (Phenergan®), ondansetron (Zofran®)
  - No dose adjustment necessary in CKD or ESRD
    - Less sedation with ondansetron and haloperidol
- Gastric motility promoting agent
  - Metoclopramide (Reglan®)
  - Decrease dose by 50% for CrCL < 40ml/min
    - Risk of anti-dopaminergic effects (extrapyramidal symptoms, tardive dyskinesias)

## Pruritus

- Etiology and treatment

- Uremia, osteodystrophy

- Therapies studied

- Antihistamines
      - Tricyclic antidepressant
      - Gabapentin
      - Selective serotonin reuptake inhibitor
      - Ondansetron

**Possible involved substances:**

- Histamine
- Serotonin
- Inflammatory cells
- Calcium
- Phosphorus

- Dry skin

- Topical emollients (lotions, creams, ointments)

- Medication-induced

- Antihistamines

## Pruritus - Medications

- Antihistamines

- Diphenhydramine (Benadryl®), hydroxyzine (Vistaril®)

- No dose adjustment; monitor for sedation, dry mouth, dizziness

- Tricyclic antidepressant

- Doxepin (Sinequan®)

- Initiate with low dose & monitor for anticholinergic side effects

- Gabapentin (Neurontin®)

- Initiate with low dose & monitor for sedation, dizziness, fatigue, tremor

- Adjust dosing interval and target dose based on CrCL

## Mr. Bernard - Medications

Aspirin 81mg PO daily  
 Donepezil (Aricept®) 10mg PO HS  
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 Hydrocodone/APAP (Norco®) 5/325mg PO QID  
 Tramadol (Ultram®) 50mg 1-2 tablets PO q6h PRN pain

## Case: Mr. Bernard

1. Dose adjustments
  - Gabapentin: dialyzable; dose needs to be reduced now that patient has stopped hemodialysis
    - Gabapentin dose range for CrCl  $\leq 15$ ml/min = 50-300mg PO QHS
  - Morphine: lengthen dosing interval for safer use
    - Change CCK morphine dose to 5mg PO/SL **q4h** PRN pain or dyspnea
2. Nausea
  - Possible etiologies: uremia, fluid/electrolyte imbalance, gastroparesis, medication-induced
  - Recommend to discontinue unnecessary medications: ferrous sulfate, vitamin C, simvastatin, ASA, donepezil, omeprazole
  - Recommend using CCK order: haloperidol 0.5mg PO/SL/PR every 4 hours as needed for nausea

## Case: Mr. Bernard

### 3. Fatigue

- Possible etiologies: anemia, accumulation of gabapentin, hypoglycemia, insomnia, depression, metabolic acidosis
- Discuss discontinuation of insulin glargine

### 4. Pain

- Tramadol dose not appropriate for ESRD; discontinue now that morphine is in place for PRN use
- Consider adding methadone to replace scheduled hydrocodone/APAP; once pain controlled on methadone can titrate off gabapentin

## Case: Mr. Bernard

### Updated med list

- Gabapentin 150mg PO QHS
- Methadone 2.5mg PO BID
- Senna/docusate 8.6/50mg 1 tab PO BID
- Morphine 5mg PO/SL q4h PRN pain or dyspnea
- Haloperidol 0.5mg PO/SL/PR q4h PRN nausea/vomiting or agitation
- Lorazepam 0.5mg PO/SL q4h PRN anxiety or dyspnea
- Atropine 1% ophth. sol. 2-4 drops SL q4h PRN terminal secretions
- Acetaminophen 650mg rectal suppository q4h PRN fever



## Key Concepts for Drug Dosing in ESRD

- Discontinue unnecessary medications
- Use creatinine clearance estimates for drug dosage recommendations
- Consider pharmacokinetic properties of the medication prior to initiating therapy
- Start with lower dose and/or extended dosing interval and titrate up based on response
- Know adverse reactions and monitor for signs of toxicity

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## Considerations for Safe Medication Use in Chronic Kidney Disease

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