ABSORPTION:

Factors affecting bioavailability in CKD	Drugs Affected
Gastric pH > ex// H2 blockers	• Iron • Ketoconazole
Edema of the GIT	• Furosemide
Antacids/PO4 binders (Ca^{2+}, Al^{3+})	• Ciprofloxacin • L-thyroxine
P-glycoprotein (efflux transport protein) > Inhibitors: cyclosporine, tacrolimus, clarithromycin	• Increase absorption of NOACS o Dabigatran o Rivaroxaban o Apixaban

METABOLISM:

- Differential effects on CYP450 enzymes
  - Some enzymes reduced (CYP3A4 and CYP2C9)
- Conjugation reactions (i.e. glucuronidation)

> Reduction of hepatic enzyme metabolism → accumulation of active metabolites
> Potential accumulation of active metabolites/parent compound → renal failure

CHRONIC OPIOIDS IN RENAL FAILURE:

Renal failure		Reason
Appears safe	• Fentanyl • Methadone	No active metabolites
Use carefully	Hydromorphone	↓ accumulation of active metabolite (HM-3-glucuronide)
	Oxycodone	< 10% excreted unchanged in urine
Best to avoid	Codeine	10% metabolized to morphine
	Morphine	Active metabolite (M-6 glucuronide) can be neurotoxic (myoclonus, sedation)
	Meperidine	Accumulation of active metabolite (normeperidine) causes tremors and seizures

EXCRETION = rate of filtration + rate of secretion – rate of reabsorption

GLOMERULAR FILTRATION: 10% of blood passing through glomerulus (1200 mL/min) is filtered into the renal tubule so GLOMERULAR FILTRATION RATE = 120 mL/min

- > 60,000 daltons (d) not filtered
- Highly protein bound (>90%) drugs to albumin (MW = 66,463 d) not filtered

SECRETION: competition for active transport system

- Trimethoprim, cimetidine blocks secretion of SCr → **pseudo-renal failure**
- Penicillin-probenecid interaction (both weak acids)
  - Probenecid blocks active transport of penicillin into kidney → increased penicillin levels

BOTTOMLINE: dose adjustment may be required if…

- High % (> 50%) of unchanged drug or active metabolite eliminated by kidney
- Decline in renal function > 50% (CrCl < 50 mL/min)

RENAL DRUG DOSAGE ADJUSTMENT:

1. Obtain history and relevant demographic/clinical info
2. Estimate creatinine clearance: C-G vs. eGFR
3. Review current medications
   a. Choose least nephrotoxic options
   b. Assess drug interactions
4. Determine individualized treatment regiment
5. Monitoring: drug levels
6. Revise regimen: change in pt status including renal function

THERAPEUTIC DRUG MONITORING:

- Duration > 1 week
- Narrow therapeutic range (phenytoin, AMGs, theophylline)
- Worsening or no improvement of S/S after 48h of therapy
- Drug toxicity is suspected
- Fluctuations in renal function
- If drug levels available
- If there is a known therapeutic range
- Query compliance

DISTRIBUTION:

- Altered Vd results from:
  - Altered tissue protein binding
  - **DIGOXIN**: Vd reduced by 30-50% from normal values in ESRD
    - Competitive inhibition by endogenous or exogenous substances → decrease in tissue binding → reduced Vd
    - Result:
      - ↓ absolute amount of digoxin bound to receptor
      - ↑ serum digoxin concentration
    - Consequence: reduce renal dose in renal dysfunction
  - Altered body composition
  - Decreased protein binding
    - Acidic drugs (i.e. warfarin, phenytoin): decreased
      - Significant if > 90% bound

PHENYTOIN: 90% protein bound to albumin

- Uremia:
  - ↓ albumin → increased unbound fraction → increased hepatic clearance → decreased concentration
  - ↓ binding to albumin → increased unbound fraction = more free concentration for site of action
- Result:
  - Adequate seizure control can be obtained at sub-therapeutic total concentrations
  - Signs of toxicity may appear at phenytoin levels within the usual therapeutic range
- Corrected Levels:
  - Corrected (umol/L) = $\frac{actual\ serum\ level\ (umol/L)}{0.02\ (albumin) + 0.1}$
- For uremic pts: SCr > 500 umol/L or dialysis
  - Corrected (umol/L) = $\frac{actual\ serum\ level\ (umol/L)}{0.01\ (albumin) + 0.1}$

    - Basic drugs (i.e. quinidine, lidocaine): generally unchanged protein binding

DRUG ADJUSTMENT IN CKD:

Drug Class	Adjust Dose (Stages 4, 5)	Avoid CKD (Stages 4, 5)	Safe Alternate
ACEI/ARBs		Avoid ARF, volume depleted	Okay in ESRD (dialysis)
Diabetic medication	Glyburide, Sitagliptan, Insulin	Chlorpropamide, Metformin	Gliclazide, Tolbutamide, Linagliptan
Diuretics		K-sparing, thiazides	Furosemide
Therapeutic anticoagulation	Enoxaparin (1 mg/kg daily)	Dalteparin, NOACs	Warfarin, heparin, tinzaparin (up to 30 days)
Opioid analgesics	Oxycodone, tramadol	Codeine, morphine, meperidine, propoxyphene	Hydropmorphone PRN, fentanyl, methadone
Other analgesics	Gabapentin, pregabalin	NSAIDs, COX-2 inhibitors	Low dose TCAs, acetaminophen
Laxatives		Mg-MOM PO4 – Fleet K – Fruitlax	Docusate, PEG, lactulose, stimulants (sennosides), microlax enema
Antacids	Cimetidine, ranitidine	Mg, Al – containing antacids, Bismuth	PPIs
Anti-microbials	See VA dose adjustments	Nitrofurantoin, amphotericin	Liposomal amphotericin