NEW ORAL ANTICOAGULANTS & ANESTHETIC CONSIDERATIONS
DISCLOSURE

- THE AUTHOR HAS NO FINANCIAL INVOLVEMENT OR ANY CONFLICT OF INTEREST IN THE SUBJECT MATTER
**DEFINITION**

- **Non-vitamin K antagonist Oral Anticoagulants**
- Refers to the current oral Direct thrombin inhibitors and Factor Xa inhibitors
OBJECTIVES

1. Review the blood clotting cascade and the impact of NAOC’S on the cascade

2. Identify and compare NAOC’S with Warfarin

3. Discuss drug reversal options for NAOC’S and Warfarin

4. Discuss perioperative management of patients on NOAC’S
OVERVIEW OF HEMOSTASIS

- 3 basic components:
  - Vascular wall
  - Platelets
  - Coagulation cascade

**Primary hemostasis** - vasoconstriction & platelet aggregation at site of injury

**Secondary hemostasis** - coagulation factors interact & form fibrin
HEMOSTASIS

- **First:** Blood Vessels Constrict
- **Second:** Platelet Plug Forms
- **CLOT:** Platlets + Fibrin
- **Third:** Clotting Cascade Activated
HEMOSTASIS

Step 1: Vascular spasm
- Smooth muscle contracts, causing vasoconstriction.

Step 2: Platelet plug formation
- Injury to lining of vessel exposes collagen fibers; platelets adhere.
- Platelets release chemicals that make nearby platelets sticky; platelet plug forms.

Step 3: Coagulation
- Fibrin forms a mesh that traps red blood cells and platelets, forming the clot.
BLOOD CLOT FORMATION

Blood clot formation

Clotting factor
Platelet
Fibrin

Red blood cell
HOW DO NOAC’S DIFFER FROM WARFARIN

- Mechanism of action-- direct inhibition of proteins on the clotting cascade
- More predictable pharmacokinetics leading to fixed and convenient dosing regimes
- No need for routine blood monitoring, wide therapeutic window
- Rapid onset of action/shorter duration of action
- No interaction with foods
- Low potential for drug interactions
- Less bleeding complications
- Decreased stroke risk
LIMITATIONS OF NOAC’S

- Higher costs -- drug cards available for many
- Limited monitoring -- qualitative measures available
- Lack of specific antidote
- Strict adherence to dosing regime
- Contraindicated in severe CKD
LIMITATIONS...

- **NOT INDICATED IN** **PTS** **WITH VALVULAR AFIB, MECHANICAL VALVES, OR WHEN THE INR IS WELL CONTROLLED AND STABLE (THERAPEUTIC)**

- **CONTRAINDICATED IN ESRD EVEN WITH RENAL REPLACEMENT**
CLINICAL INDICATIONS FOR THE USE OF NOAC’S

- Secondary prevention of non-valvular AFib induced stroke or TIA
- Prevent systemic emboli in non-valvular Afib
- Thrombo-prophylaxis in post hip and knee replacement
- Treat DVT and PE
2 BROAD CATEGORIES OF NAOC’S

- DIRECT THROMBIN INHIBITORS (DTI’S)
  - Factor Iia inhibitor
  - 1ST was Exanta, taken off the market in 2004 due to serious liver injury
  - Pradaxa (Dabigatran) FDA approved in October 2010
  - INHIBITS BOTH FREE & FIBRIN-BOUND THROMBIN thus blocks conversion of fibrinogen to fibrin
  - Results in reduced thrombin-mediated platelet aggregation

- FACTOR Xa INHIBITORS
  - Xarelto (Rivaraxaban) July 2011
  - Eliquis (Apixaban) December 2012
  - Savaysa (Edoxaban) January 2015
  - Betrixaban-in trials now, aimed at severe renally impaired but not on dialysis pts, eliminated mainly hepatically not renally

- TARGET SPECIFIC, INHIBIT PLATELET & FIBRIN CLOT FORMATION VIA SELECTIVE INHIBITION OF BOTH FREE AND CLOT-BOUND FACTOR Xa
NOAC’S

- DTI (IIa) - inactivates clot-bound and soluble thrombin
- FACTOR Xa INHIBITORS - inhibits the conversion of prothrombin to thrombin

- LOW PROTEIN BINDING
- PREDICTABLE
- FIXED DOSING
  - BID
- HIGH PROTEIN BINDING
- PREDICTABLE
- FIXED DOSING
  - XARELTO: BID
  - ELIQUIS & SAVAYSA: OD
### Key Features of NOAC’s Compared to Warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Pradaxa</th>
<th>Xarelto</th>
<th>Eliquis</th>
<th>Savaysa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>VIT K Antagonist</td>
<td>DTI</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
</tr>
<tr>
<td>Dosing Regime</td>
<td>Varies</td>
<td>BID</td>
<td>OD</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td>1/2 Life Hours</td>
<td>40 HRS</td>
<td>12-14 HR</td>
<td>5-11HR</td>
<td>8-15HR</td>
<td>8-14HR</td>
</tr>
<tr>
<td>Elimination</td>
<td>92% Renal</td>
<td>80% Renal/20% Fecal</td>
<td>66% Renal/33% Fecal</td>
<td>25% Renal/75% Fecal</td>
<td>35% Renal/65% Fecal</td>
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<tr>
<td>Monitoring</td>
<td>PT/INR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>aPTT ++</td>
<td>aPTT +/-</td>
<td>aPTT +/-</td>
<td>aPTT +/-</td>
<td>aPTT +/-</td>
</tr>
<tr>
<td></td>
<td>PT/INR+TT+</td>
<td>PT/INR++</td>
<td>PT/INR++</td>
<td>PT/INR++</td>
<td>PT/INR++</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vit K1</td>
<td>Part/Hemodialysis</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
</tr>
</tbody>
</table>
TIME TILL FULL THERAPEUTIC EFFECT

- **WARFARIN**
  - 5 DAYS AFTER INITIATION OF TREATMENT

- **NOAC’S**
  - IN LESS THAN 24 HOURS AFTER INITIATION OF TREATMENT

- **DO NOT GIVE THESE TOGETHER, DUPLICATION OF THERAPY, MAY USE BRIDGING TECHNIQUE**
WARFARIN

- Suppresses the synthesis of biological Vit-K dependent clotting factors (II, VII, IX, X) and the regulatory factors Protein S & C
- INR changes within 1-2 days
- Takes up to 5 days for full antithrombotic effect
- Preferred anticoagulant with pts with mechanical heart value
WARFARIN-TARGET

Warfarin inhibits early steps in the clotting pathway.

Blood vessel damage → Protein XII activation → Protein XI activation → Protein X activation → Thrombin activation.

Fibrinogen → Fibrin mesh (the clot).

Intrinsic Pathway:
- XII → XIIa
- XI → XIa
- X → Xa
- IX → IXa
- VIII → VIIIa
- VII → VIIa
- Xa → THROMBIN

Extrinsic Pathway:
- II → IIa
- V → Va
- Fibrinogen → FIBRIN
- Fibrin Clot

DABIGATRAN exits to the right of the intrinsic and extrinsic pathways.
Figure 1: Action of Anticoagulants in the Coagulation Cascade

Intrinsic pathway
- IXa
- Xla
- Xla (Thrombin)

Extrinsic pathway
- TF
- VIIa
- VIIIa
- Xa
- IIa

Heparins via antithrombin
- Xa, IIa

Warfarin
- II, VII, IX, X

Fondaparinux
- Idraparinux
- Xabans
- Xa

Hirudin
- Bivalirudin
- Argatroban
- Dabigatran...

Note that edoxaban is not registered for use in the EU and the USA at the time of publication.
Extrinsic Pathway

Factor VIIa
Tissue Factor
Phospholipids

Factor IX – Factor IXa

Intrinsic Pathway

Factor IXa
Factor VIIIa
Phospholipids

Direct Factor Xa Inhibitors
Rivaroxaban
Apixaban

Indirect Factor Xa Inhibitors
- Antithrombin
- Fondaparinux
- Idraparinux

Factor X

Direct Thrombin Inhibitors
- Hirudin
- Argatroban
- Bivalirudin
- Dabigatran

Factor Xa

Prothrombin
Thrombin
Fibrinogen
Fibrin
WARFARIN REVERSAL GUIDELINES

AMERICAN HEART ASSOCIATION
&
AMERICAN COLLEGE OF CARDIOLOGY
RECOMMENDATIONS
LEVEL 1

- FRESH FROZEN PLASMA (FFP) FOR EMERGENCY REVERSAL OF ELEVATED INR’S
LEVEL 2

- VIT K (phytonadine) admin BASED ON:
  - INR
  - RISK OF BLEEDING
  - FUTURE NEED FOR ANTICOAGULATION

- VIT K EITHER PO OR IV, never IV PUSH
  - 1--2 MG IV OR 2–5 MG PO

- ONLY USE VIT K FOR MOST SERIOUS BLEEDS
LEVEL 3

- INITIAL DOSE OF FFP BASED ON RISK OF BLEEDING
  - LOW RISK = FFP 2 UNITS
  - HIGH RISK OR ACTIVE BLEEDING = FFP 4 UNITS
  - RECHECK INR 1 HOUR AFTER FFP

- PROTHROMBIN COMPLEX CONCENTRATE (PCC):
  - CONTAINS CLOTTING FACTORS II, VII, IX, AND X AS WELL AS THE THROMBIN INHIBITORS PROTEINS C & S
  - ADMINISTER IF INR >2 AND EVIDENCE OF INTRACRANIAL BLEED BY CT SCAN

- FACTOR VIII INHIBITOR BYPASS ACTIVITY (FEIBA):
  - CONTAINS CLOTTING FACTORS II, VII, IX, AND X
  - ADMINISTER 1000 UNITS IV PUSH OVER 5 MIN
    - REPEAT INR IN 30 MINUTES

- DO NOT ADMIN VIT K TO PTS WITH PROSTHETIC VALVES, ONLY LOW DOSES (1 MG) SHOULD BE USED IF ABSOLUTELY NECESSARY
REVERSAL OF DTI’S

- MAY TRY HEMODIALYSIS:
  - LOW PROTEIN BINDING (35%)
  - RENAL ELIMINATION (92%)

#ACTIVATED CHARCOAL CAN BE USED IF MEDICATED WITHIN 2 HOURS OF ADMINISTRATION OF DTI
REVERSAL OF NOAC’S

4F- PCC (PROTHROMBIN COMPLEX CONCENTRATE)-life threatening bleeds
- 25-50 UNITS/KG

FEIBA (ACTIVATED PROTHROMBIN COMPLEX CONCENTRATE, aPCC)
- 50 UNITS/KG UP TO MAX OF 200 UNITS/KG/DAY IN DIVIDED DOSES

ANTIFIBRINOLYTIC AGENTS (EX: TRANEXAMIC ACID (TXA))
- 1 GM IV WITHIN 3 HOURS OF SURGERY, REPEAT q 8 HOURS AS NEEDED

RECOMBINANT ACTIVATED FACTOR VII (rFVIIa)
- 90MCG/KG

- THESE THERAPEUTIC OPTIONS ARE NOT VALIDATED BY LARGE - SCALE TRIALS

- BEST REVERSAL IS TIME - STOP ADMIN OF DRUG IMMEDIATELY

- NEW REVERSAL AGENTS ON THE HORIZON
## NAOC Antidotes in Clinical Trials

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anexanet (PRT064445)</td>
<td>Recombinant Protein, targets &amp; sequesters direct &amp; indirect factor Xa inhibitors with high specificity, bolus &amp; infusion dosing</td>
</tr>
<tr>
<td>Aripazine (PER977)</td>
<td>Antidote for factor Xa inhibitors, DTI’s, LMWH, &amp; fondaparinux reversal effect is through direct binding to the anticoagulant</td>
</tr>
<tr>
<td>Idarucizumab (BI655075)</td>
<td>Antidote for DTI’s, humanized antibody fragment most likely to be released in the near future</td>
</tr>
</tbody>
</table>
TESTS FOR ANTICOAGULATION

- **WARFARIN---PT/INR**

- **aPTT---** activated partial thromboplastin time, may help assess presence of Pradaxa, if aPTT level (12-24 hours after LD) exceeds 2 x the upper limit of normal this is associated with high risk of bleeding, Ecarin time also correlates with Pradaxa blood concentration.

- **PT---** may help assess presence of factor Xa inhibitors, normal PT would indicate absence of drug in body.
CLOTTING CASCADE

LAB TESTS

The Clotting Cascade

Intrinsic Pathway (I.P)
- XII → XI → IX → VIII → X + V
- Prothrombin (II)

Extrinsic Pathway (E.P)
- VII → X + V
- Thrombin

- PTT: measures I.P
- PT/INR: measures E.P

Clot Formation
- Fibrinogen (I)
- Factor XIII
- Clot Formation
QUANTITATIVE TESTING FOR NOAC’S

- These tests do exist
- Diluted – Thrombin Time for DTI’s
- Chromogenic assays for Factor Xa inhibitors
- Not routinely available, expensive
- No data to prove they are safe for elective or emergency surgery use
- Normalized aPTT and PT prior to surgery has not been validated as safe to proceed
PERIOPERATIVE MANAGEMENT

- BASED ON:
  - URGENCY OF SURGERY
  - LEVEL OF BLEEDING RISK
  - CURRENT RENAL FUNCTION
INSTITUTIONAL GUIDELINES

- HIGHLY RECOMMENDED TO HAVE POLICIES IN PLACE

- MOST IMPORTANT RECOMMENDATIONS:
  - STOP ALL NOAC’S WHEN EMERGENCY SURGERY IS INDICATED
  - KNOW EXACT TIME OF LAST DOSE
  - DO THEY TAKE OD OR BID DOSING AND DOSE AMT
STOP ALL NOAC’S 12-24 HOURS PRIOR TO THE PROCEDURE

- DEPENDING ON ONCE OR TWICE A DAY DOSING & RENAL FUNCTION

2-3 DRUG HALF-LIVES BETWEEN LAST DOSE AND SURGERY

- EX: PRADAXA HALF LIFE IS 12 HRS (STOP MINIMUM OF 24 HRS BEFORE PROCEDURE)
RECOMMENDATION...

- FOR SPINAL & EPIDURAL OR MAJOR SURGERY:
  - STOP ALL NOAC’S 48 HOURS BEFORE, IN PTS WITH NORMAL RENAL FUNCTION
  - LONGER PERIOD OF TIME IN PTS WITH RENAL IMPAIRMENT
  - CHECK aPTT IN PTS ON DTI
  - CHECK PT IN PTS ON FACTOR Xa INHIBITORS
  - IF LEVELS ARE NORMAL: SUGGESTIVE OF VERY LOW DRUG SERUM CONCENTRATION
HIGH BLEEING RISK PROCEDURES

- STOP 4 OR 5 DRUG HALF-LIVES BETWEEN LAST DOSE AND SURGERY
- STOP MEDICATION AT LEAST 48 HOURS BEFORE SURGERY
NOAC’S AND CrCl

- RISK FOR BLEEDING IS AFFECTED BY CrCl
- DECREASED DOSAGE OF NOAC’S ARE NEEDED AS CrCl DECLINES
- EXCRETION OF NOAC’S BY THE KIDNEYS REQUIRES CLOSE MONITORING OF CrCl TO AVOID EXCESSIVE DRUG ACCUMULATION IN THE BODY
- CrCl OF 15-30 DTI’S ARE NOT INDICATED
  - HIGH RENAL ELIMINATION
- CrCl OF <15 DTI’S AND FACTOR Xa ARE NOT INDICATED FOR USE
CrCl AND PREOP INTERRUPTION OF NOAC’S

<table>
<thead>
<tr>
<th>CrCl</th>
<th>PRADAXA</th>
<th>PRADAXA</th>
<th>FACTOR Xa INHIBITOR</th>
<th>FACTOR Xa INHIBITOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOW RISK</td>
<td>HIGH RISK</td>
<td>LOW RISK</td>
<td>HIGH RISK</td>
</tr>
<tr>
<td>NORMAL ≥60</td>
<td>&gt;24 HOURS</td>
<td>&gt;48 HOURS</td>
<td>&gt;24 HOURS</td>
<td>&gt;48 HOURS</td>
</tr>
<tr>
<td>50-60</td>
<td>&gt;36 HOURS</td>
<td>&gt;72 HOURS</td>
<td>&gt;24 HOURS</td>
<td>&gt;48 HOURS</td>
</tr>
<tr>
<td>30-50</td>
<td>&gt;48 HOURS</td>
<td>&gt;96 HOURS</td>
<td>&gt;24 HOURS</td>
<td>&gt;48 HOURS</td>
</tr>
<tr>
<td>15-30</td>
<td>NOT INDICATED</td>
<td></td>
<td>≥36 HOURS</td>
<td>&gt;48 HOURS</td>
</tr>
<tr>
<td>≤15</td>
<td>DO NOT USE</td>
<td></td>
<td>DO NOT USE</td>
<td></td>
</tr>
</tbody>
</table>
WHEN TO RESUME NOAC’S AFTER SURGERY

- LOW BLEEDING RISK SURGERY
  - RESUME ON DAY AFTER SURGERY
  - WAIT FOR MINIMUM OF 24 HOURS POSTOP TO RESUME

- HIGH BLEEDING RISK SURGERY
  - RESUME 2-3 DAYS AFTER SURGERY
  - WAIT FOR MINIMUM OF 48-72 HOURS POSTOP TO RESUME
THANK YOU!

RELAX
DISCLOSURE

THE AUTHOR HAS NO CONFLICT OF INTEREST OR FINANCIAL INVOLVEMENT IN THE SUBJECT MATERIAL
DEFINITION

- ALSO CALLED CHRONIC KIDNEY FAILURE

- A GRADUAL DECREASE IN KIDNEY FUNCTION OR KIDNEY DAMAGE THAT PERSISTS FOR 3 OR MORE MONTHS, PROGRESSIVE & IRREVERSIBLE

- EVIDENCED BY URINALYSIS, HISTOLOGIC AND IMAGING ABNORMALITIES

- CLASSIFIED ACCORDING TO STAGES

- LAST STAGE OF KIDNEY FAILURE (ESRD), REQUIRES DIALYSIS (ARTIFICIAL FILTRATION) OR TRANSPLANT
OBJECTIVES

- Identify the prevalence of CKD in the USA and its causes
- Describe the clinical findings associated with the 5 stages of CKD
- Identify the pathophysiological and pharmacological changes relevant to anesthesia admin in patients with CKD
- Consider anesthesia techniques that minimize risk for CKD patients
PREVALENCE OF CKD

- 1 in 7 US adults (26 million)
- Approx 435,000 have ESRD/HD (2010)
- Most prevalent of chronic medical conditions
  - Largely related to glomerular filtration abnormalities
- Less than 2 percent of children have ESRD
  - Largely due to congenital kidney disease
- Predicted by CDC that CKD will affect more than half of all Americans aged 30 to 64 over the next 20 yrs
IN 2010
- ESRD COST MEDICARE 33 BILLION DOLLARS
- EARLIER STAGES OF CKD COST 48 BILLION

ANNUAL MORTALITY RATE FOR ESRD: 24%
- HEART DISEASE IS THE MAJOR CAUSE OF DEATH IN THESE PATIENTS

SIMPLE TESTS CAN DETECT CKD

- SERUM CrCl, BUN
- URINALYSIS: CREATININE & PROTEIN
KIDNEY

- HAVE 1 MILLION NEPHRONS / KIDNEY
- GFR ESTIMATES
  - HOW MUCH BLOOD PASSES THRU THE GLOMERULUS / MIN
  - GLOMERULUS FILTERS ALL WASTES FROM THE BLOOD
  - RENAL TUBULES CHANGE FILTRATE INTO URINE BY REABSORPTION & SECRETION
- 2 MAIN FUNCTIONAL UNITS
  - GLOMERULUS
  - RENAL TUBULES
GFR CALCULATION

- COCKCROFT-GAULT

  MEN:  \( \text{CrCl (ML/Min)} = \frac{(140 - \text{AGE}) \times \text{WT (KG)} \times \text{Scr}}{0.81} \)

  WOMEN: MULTIPLY BY 0.85
# Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90+</td>
<td>Normal Kidney Function, Urine, Structural &amp; Genetic Findings Point</td>
<td>Observe, control B/P, Lifestyle changes (Lower Chol, Stop Smoking, Weight Management, Exercise), Monitor Urine-Protein, Creatinine</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Decreased Kidney Function + Stage 1</td>
<td>Same as Stage 1, may require more freq monitoring</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderately Reduced Kidney Function</td>
<td>Same + Q 3-6 months monitoring of GFR, Urinary Protein, Hg, Cardiac Consult (20 percent risk of CV event over 10 years), Update Immunizations</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severly Reduced Kidney Function</td>
<td>Prepare for ESRD, Monitor Creatine, Protein, Phosphorus, Calcium, K+ Every 3 Months</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>ESRD, Severe Dysfunction</td>
<td>Dialysis or Transplant</td>
</tr>
</tbody>
</table>
CAUSES OF CKD

- 2/3RDS OF ALL CKD IS DUE TO:
  - HYPERTENSION (25 %)
  - DIABETES (40 %)

- 3RD MOST COMMON CAUSE
  - GLOMERUONEPHRITIS, CHRONIC INFLAMMATION

- INHERITED DISEASES:
  - EX: POLYCYSTIC DISEASE

- CONGENITAL MALFORMATIONS

- OBSTRUCTIONS, CONGENITAL OR ACQUIRED

- LUPUS & OTHER IMMUNE DISORDERS

- RECURRENT UTI’S & KIDNEY INFECTIONS
# Pathophysiologic Changes Associated with CKD

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>HTN (UNCONTROLLED), CHF, PERIPHERAL EDEMA, PERICARDITIS, CAD, ARRHYTHMIAS, ANGINA, LVH</td>
</tr>
<tr>
<td>HEMATOLOGIC</td>
<td>ANEMIA (ERYTHROPOEITIN DYSFUNCTION), PLATELET DYSFUNCTION BUT ONLY MILDLY REDUCED COUNTS, LEUKOCYTE (IMMUNOLOGIC DYSFUNCTION), INCREASED INFECTION RISK</td>
</tr>
<tr>
<td>NEUROLOGIC</td>
<td>ENCEPHALOPATHY, PERIPHERAL &amp; AUTONOMIC NEUROPATHY, PERSONALITY CHANGES, AGITATION, SEIZURES, MENTAL CONFUSION</td>
</tr>
<tr>
<td>ENDOCRINE</td>
<td>HYPERPARATHYROIDISM, ADRENAL INSUFFICIENCY</td>
</tr>
<tr>
<td>RESPIRATORY</td>
<td>PNEUMONITIS, PULM INFECTIONS, PULM EDEMA</td>
</tr>
<tr>
<td>GI</td>
<td>BLEEDING, N &amp; V, DELAYED GASTRIC EMPTYING, STRESS ULCERS, MALNUTRITION, ACIDOSIS, ELECTROLYTE IMBALANCES (HIGH K+,</td>
</tr>
</tbody>
</table>
METABOLIC CHANGES ASSOCIATED WITH CKD

- **DECREASES**
  - HEMOGLOBIN / HEMATOCRIT
  - BICARB
  - CALCIUM
  - SODIUM
  - ALBUMIN
  - CALCITROL

- **INCREASES**
  - BUN/CRT
  - PHOSPHATE
  - PTH
  - TRIGLYCERIDES
  - POTASSIUM
  - MAGNESIUM
METABOLIC CHANGES...

- MONITOR & TREAT BIOCHEMICAL ABN:
  - ANEMIA
  - METABOLIC ACIDOSIS
  - MINERAL METABOLISM
  - DYSLIPIDEMIA
  - NUTRITION
MOST SIGNIFICANT CHANGE WITH ADVANCING CKD...

- **METABOLIC ACIDOSIS**
  - IN LATER STAGE 3 & STAGE 4 & 5
  - A MIXTURE OF NORMAL AND INCREASED ANION GAP
  - KIDNEYS ARE UNABLE TO PRODUCE ENOUGH AMMONIA IN THE PROXIMAL TUBULES TO EXCRETE ACID INTO THE URINE IN THE FORM OF AMMONIUM

- **CAUSES**
  - PROTEIN-ENERGY MALNUTRITION
  - LOSS OF LEAN BODY MASS
  - MUSCLE WEAKNESS
  - INTERFERENCE WITH VIT D METABOLISM
  - RENAL OSTEODYSTROPHY

- LEADS TO RAPID FIBROSIS OF KIDNEY TISSUE AND MORE RAPID PROGRESSION OF KIDNEY DISEASE
HOW DO WE CARE FOR THESE PATIENTS
SYSTEM APPROACH TO CARE

RENAL SYSTEM
GOAL IS TO ID AND OPTIMIZE PRE-EXISTING PATHOPHYSIOLOGY TO MINIMIZE RISK

REQUIRES:

- ANESTHESIA
- SURGEON
- NEPHROLOGIST
- CARDIOLOGIST, ENDOCRINOLOGIST, & PULMONOLOGIST, IF INDICATED
TYPICAL PREOP TESTING

- RENAL PROFILE: NA, K, CL, BUN, Cr, Ca, & BICARB
- CBC
  - ANEMIA
  - PLATELET FUNCTION
- ABG’S IF BICARB IS BELOW 18 mEq / L
- BLEEDING TIME & COAGULATION STUDIES
  - BLOOD THINNERS
  - HEPARIN USED DURING HEMODIALYSIS
- PHYSICAL EXAM
  - EMPHASIS ON VOLUME STATUS
  - FLUID OVERLOAD OR HYPOVOLEMIA
  - CHECK WEIGHT AND COMPARE TO THEIR NORM
- CXR-FLUID STATUS
- EKG-ARRHYTHMIAS, BASELINE, VENTRICULAR HYPERTROPHY
OTHER CONSIDERATIONS...

- FLUID RESTRICTIONS
- URINE OUTPUT—YES OR NO
- RENAL REPLACEMENT THERAPY
  - DIALYSIS - REGIME
  - LAST TREATMENT
- TYPE OF DIALYSIS AS RELATES TO SURGICAL NEED
  - IF PERITONEAL DIALYSIS MAY NEED TEMPORARY IJ CATHETER PLACEMENT FOR DIALYSIS IF ABDOMINAL SURGERY
RENAL REPLACEMENT THERAPY

- **TIMING OF DIALYSIS**
  - HEMODIALYSIS OR PERITONEAL DIALYSIS
  - 12-24 HRS PRIOR TO SURGERY IS IDEAL
  - NEPHROLOGIST MAY ALTER DIALYSATE TO INFLUENCE THE AMOUNT AND COMPOSITION OF FLUID REMOVED

- **EFFECTS OF DIALYSIS:**
  - FLUID DEPLETION
    - REDISTRIBUTION OF EXTRAVASCULAR SPACES RESULTS IN DEPLETION OF INTRAVASCULAR VOLUME
  - ELECTROLYTE DISTURBANCES
    - HYPERKALEMIA, HYponATREMIA, HYPOCALCEMIA, HYPERMAGNESEMIA
  - RESIDUAL ANTICOAGULATION
    - FROM HEPARINIZATION OF THE DIALYZER CIRCUIT
  - HYPOTENSION
    - FROM THE VASODILATING EFFECTS OF ACETATE DIALYSATE SOLUTIONS
  - RAPID REMOVAL OF FLUID
  - AUTONOMIC NEUROPATHY
  - HYPOXEMIA
POST-DIALYSIS MEASUREMENT OF SERUM ELECTROLYTES IS REQUIRED BEFORE SURGERY AS DIALYSIS INDUCED ELECTROLYTE IMBALANCES PREDISPOSES PATIENT TO INTRAOP CARDIAC ARRHYTHMIAS & POTENTIAL CARDIAC ARREST

- EKG MANIFESTATIONS OF HYPERKALEMIA INCLUDE:
  - BRADYCARDIA
  - PR PROLONGATION
  - QRS WIDENING
  - PEAKED T WAVES
  - AV BLOCK
<table>
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<th>SYSTEM</th>
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<td>ANTACID, H2 BLOCKERS-MAY PROLONG QT ALTER ANESTHESIA TECH TO PROTECT AIRWAY</td>
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<td>CAUSES INTRAOP HEMODYNAMIC INSTABILITY, MAY REQUIRE INVASIVE MONITORING &amp; ANESTHETIC DRUG DOSE ALTERATIONS</td>
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<td>HEMATOLOGIC</td>
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<td>DETERMINE ACCEPTABLE PERIOP Hgb LEVELS, BLD COMPONENTS THAT MAY NEED ORDERED, ADMIN OF ERYTHROPOIETIN TO CORRECT ANEMIA, IRON REPLACEMENTS</td>
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<td>ANTIMIOTICS, STEROIDS, MINIMIZE INVASIVE PROCEDURES</td>
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</table>
3 mechanisms by which kidneys excrete drugs:
- Filtration
- Passive reabsorption
- Active secretion

Other influences on kidney successful excretion of waste:
- Drug particle size & charge
- Protein binding
- Water solubility
- Urine pH
ANESTHETIC MANAGEMENT OF THE PATIENT WITH ADVANCED RENAL DYSFUNCTION

- PREMEDS
  - SENSITIVE TO CNS DEPRESSANTS

- SAFE TO USE MIDAZOLAM
  - NO ACTIVE METABOLITES
  - ONLY SLIGHTLY PROLONGED HALF-LIFE WITH RENAL FAILURE
  - REDUCE DOSE
OTHER MEDS IN PRE-PROCEDURE PERIOD

- ACE INHIBITORS (EX: enalapril) & ANGIOTENSIN II ANTAGONISTS (EX: larsartan)
  - USED TO TREAT HTN IN CKD
  - ASSOCIATED WITH INTRAOP HYPOTENSION
  - STOP AT LEAST 10 HRS BEFORE SURGERY TO REDUCE RISK OF POST-INDUCTION HYPOTENSION
ASPIRATION PROPHYLAXIS

- **H2 BLOCKER:**
  - INDICATED FOR N & V
  - GI REFLUX

- **METOCLOPRAMIDE:**
  - ACCELERATES GASTRIC EMPTYING
  - PREVENT N & V
  - DECREASE ASPIRATION RISK
DRUGS THAT INCREASE INTRAOP BLEEDING

- **ANTIPLATELET AGENTS**
  - STOP 72 HOURS BEFORE SURGERY

- **OTHER AGENTS THAT HAVE PROFOUND ANTIPLATELET EFFECTS ON ESRD PATIENTS ARE**
  - DIPHENHYDRAMINE (BENADRYL)
  - NSAIDS (INDUCES AFFERENT RENAL ARTERIOLAR VASOCONSTRICTION THUS LIMITING GLOMERULAR BLOOD FLOW)
  - CHLORDIAZEPoxide (LIRIUM)
  - CIMETIDINE (TAGAMET)
ANTIBIOTIC PROPHYLAXIS

- VANCOMYCIN ROUTINELY USED
  - TO REDUCE THE DEVELOPMENT OF DRUG RESISTANT BACTERIA
  - WORKS ON GRAM + BACTERIA
  - BACTERIA BECOMING RESISTENT TO THIS DRUG
  - REDUCE DOSE

- FIRST GENERATION CEPHALOSPORIN (EX: KEFLEX, OR ANCEF)
  - IS NEW DRUG OF CHOICE
  - NO DOSING ADJUSTMENTS INDICATED
PROPOFOL & ETOMIDATE

- DECREASED PROTEIN BINDING
- ENHANCED PHARMACOLOGICAL EFFECTS
- DECREASE DOSAGE
- LONGER LASTING EFFECT
KETAMINE

- MINIMAL RENAL EFFECTS

- SOME ACTIVE HEPATIC METABOLITES ARE DEPENDENT ON RENAL EXCRETION AND CAN ACCUMULATE IN SEVERE RENAL FAILURE

- SECONDARY HYPERTENSIVE EFFECTS MAY BE UNDESIRABLE IN HYPERTENSIVE RENAL PATIENTS
IV MUSCLE RELAXANTS

- **NEUROMUSCULAR BLOCKING AGENTS**

  - **SUCCINYLCHOLINE**
    - SAFE IF NORMOKALEMIC
    - IF HAD DIALYSIS WITHIN LAST 24 HOURS
      - CHECK K+
    - INADVISABLE IF K+ IS > 5

  - **ATRACURIUM & cisATRACURIUM**
    - HOFFMAN ELIMINATION
    - NOT RENAL OR HEPATIC DEPENDENT FOR EXCRETION
    - ONSET, DURATION AND RECOVERY ARE THE SAME AS NORMAL RENAL FUNCTION PATIENTS
    - MAY BE DRUGS OF CHOICE FOR SEVERE CKD PTS
NMBA’S…

- **VECURONIUM**
  - 20 - 30 PERCENT EXCRETED BY KIDNEY
  - REDUCED RENAL CLEARANCE WITH CKD
  - INCREASED ACCUMULATION
  - PROLONGED ACTION
  - REDUCE DOSE

- **ROCURONIUM**
  - 33 PERCENT EXCRETED BY KIDNEY
  - DURATION OF ACTION, TIME TO RECOVERY PROLONGED
  - REDUCE DOSE
  - USED IN RENAL TRANSPLANT
  - USED BECAUSE OF IT’S RAPID ONSET
    * BENEFICIAL IN RENAL PTS DUE TO THEIR AUTONOMIC NEUROPATHY AND DELAYED GASTRIC EMPTYING
MUSCLE RELAXANT REVERSALS

- **NEOSTIGMINE**
  - Clearance is reduced
  - Half-life prolonged
  - Have increased parasympathomimetic response (SB, AV block)
  - Use glycopyrolate instead of atropine
    - Decreased parasympathomimetic response

- **SUGAMMADEX**
  - Encapsulates NDMR
  - Does not bind to plasma proteins
  - Excreted unchanged in urine within 16 hours
  - No reliance on renal excretion for efficacy
NON-OPIOIDS

- NKF RECOMMENDS:
  - ACETAMINOPHEN
  - ANALGESIC OF CHOICE
  - DIALIZABLE
  - INCREASE DOSING INTERVAL TIMING
    - 5 INCTIVE METABOLITES
    - RENALLY EXCRETED

- IV, PO, RECTAL DOSING WITH SURGERY DECREASES OPIOID CONSUMPTION
OPIOIDS

- HAVE ANTIDIURETIC EFFECT - CAUSING URINARY RETENTION

- HAVE NO DIRECT TOXIC EFFECTS ON THE KIDNEY
OPIOID SUMMARY

- SAFEST TO USE IN CKD INCLUDING HD PTS:
  - FENTANYL
  - REMIFENTANIL
  - HYDROCODONE
  - HYDROMORPHONE

- AVOID
  - MORPHINE
  - MEPERIDINE
  - CODEINE
OPIODS ...

- **FENTANYL**
  - Considered the safest for CKD
  - No active metabolites
  - Extensive hepatic metabolism
  - Clearance is reduced in CKD
  - Reduce dose

- **ALFENTANIL**
  - Elimination half-life and plasma clearance unaltered in CKD
  - Reduced protein binding, thus increased free fraction of alfentanil
  - Reduce dose
  - Dose interval unchanged
**OPIOIDS...**

- **REMFENTANIL**
  - Not dependent on renal function for excretion
  - Rapid ester hydrolysis in blood
  - HD patients
    - Reduce dose due to prolonged half-life
  - Use lower infusion rates but recovery is not significantly prolonged

- **OXYCODONE**
  - Parent compound and metabolites accumulate in renal failure
  - Reduce dose
  - Increase dose interval time
OPIOIDS...

- MORPHINE
  - 5% of drug is broken down into M6G
  - Which has potent analgesic effects
  - Causes delayed resp & CNS depression
  - Best to avoid but can be used in small doses

- MEPERIDINE
  - Active metabolite normeperidine causes seizures in CKD
  - Avoid
CODEINE & HYDROCODEINE

- **DO NOT USE** ON HD PATIENTS
- LOW DOSE IN CKD, NONE IN ESRD
- ELIMINATION HALF-LIFE IS SIGNIFICANTLY PROLONGED
- ALL ACTIVE METABOLITES ARE EXCRETED IN URINE
- CONVENTIONAL DOSES HAVE RESULTED IN CNS DEPRESSION
INHALATION AGENTS

- ADVANTAGES:
  - ELIMINATION IS NOT RENALLY DEPENDENT
  - MINIMAL DIRECT EFFECTS ON RBF
  - POTENTIATE NMBA’S
    - REDUCE THEIR DOSES
  - LOW-FLOW ADMINISTRATION IS POSSIBLE
  - GOOD AIRWAY CONTROL
  - B/P CONTROL
  - FIO2 CAN BE INCREASED
    - N2O IS NOT NECESSARY

- DISADVANTAGE:
  - INDUCE A REDUCTION IN RENAL BLOOD FLOW IN UP TO 50% OF PATIENT, MORE PROGRESSIVE THE CKD THE GREATER CHANCE OF REDUCED RBF
INHALATION AGENTS...

- **SEVOFLURANE**
  - Elevated fluoride levels
  - Rate of elimination did not differ from patients with normal kidney function
  - No significant change in kidney function
  - Suitable to use

- **ENFLURANE**
  - Greater inorganic fluoride levels
  - Causes vasopressin-resistant polyuria
  - Case reports show increased chance of renal failure after exposure if have CKD
  - Best to avoid in CKD
INHALATION AGENTS...

- DESFLURANE & ISOFLURANE
  - NO RENAL TOXICITY
  - NO CHANGE IN BUN & CREATININE POSTOP
  - LEAST EFFECT ON CARDIAC OUTPUT
  - SAFE TO USE WITH CKD
INTRAOPERATIVE FLUID MANAGEMENT

- MAINTAIN EUVOLEMIA
  - MOST HAVE CHRONIC ACIDOSIS
  - PRONE TO EXTRACELLULAR VOLUME LOAD

- NSS INSTEAD OF LR SOLUTION
  - LR HIGHER K+ CONTENT (4 MEQ/L)
  - RECENT STUDIES INDICATE THAT NSS IS HYPERTONIC & HYPERCHLOREMIC
    - CAN LEAD TO METABOLIC ACIDOSIS
    - EXACERBATE HYPERKALEMIA

- LR IS AN ACCEPTABLE CHOICE IF NOT GIVEN IN LARGE VOLUMES

AVOID GLUCOSE SOLUTIONS -GLUCOSE INTOLERANCE ASSOCIATED UREMIA
MORE FLUID CONSIDERATIONS

- **BLOOD ADMIN**
  - Down side to blood product admin is antibody formation which can lead to a decreased future chance for successful transplant
  - Use irradiated blood
    - Prevents graft vs host disease
    - Required for RBC and platelet admin
      - Due to T-lymphocytes being active in these

- **BLOOD ADMIN CAN ALSO LEAD TO HYPERKALEMIA**

- **ANEMIA**
  - Caused by decreased renal production of hormone erythropoietin
  - Also reduced life span of RBC’s due to hemolysis from build up chemicals in the blood
REGIONAL ANESTHESIA

CONCERNS ARE RELATED TO
- PRESENCE OF PERIPHERAL NEUROPATHIES
- INCREASED BLEEDING RISK, COAGULATION DISORDERS
- ANXIETY, PSYCHOLOGIC INTOLERANCE
- LENGTH OF PROCEDURE-PROLONGED OR SHORT
- HYPOTENSION WITH SYMPATHETIC BLOCK
  - Fluid volume replacement
- RISK OF INFECTION
- METABOLIC ACIDOSIS- MAY INCREASE LOCAL TOXICITY

ADVANTAGES
- MINIMAL CHANGES IN RENAL HEMODYNAMICS
- AVOID MOST OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PROBLEMS ASSOCIATED WITH GENERAL ANESTHESIA AND SEDATIVES
- IMPROVED POSTOP PAIN SCORES
- MAY REDUCE MORTALITY
AV-FISTULA

- USING REGIONAL BLOCKS
  - INTERSCALENE
  - SUPRACLAVICULAR
  - INDUCES VAODILATATION IN UPPER EXTREMITY
  - IMPROVES BLOOD FLOW
  - RESULTS IN LOWER AV-FISTULA FAILURE RATES
LOCAL ANESTHETICS

- LIDOCAINE IS SAFE AS AN INFILTRATION DRUG, A TOPICAL GEL OR PATCH, OR IV AS A CONTINUOUS INFUSION
  - HALF-LIFE 90-120 MIN
  - ELIMINATION UNAFFECTED BY RENAL DISEASE
  - PROLONGED WITH HEPATIC IMPAIRMENT
  - IV DOSING AS INFUSION---PAIN RELIEF DUE TO INHIBITING AFFERENT PAIN FIBERS VIA SODIUM CHANNEL BLOCKADE IN SPINAL CORD
MORBIDITY & MORTALITY IS INCREASED INPTS WITH ADVANCED CKD

MORBIDITY RATES FOR BOTH CARDIAC AND GENERAL SURGERY IN PATIENTS WITH ESRD RANGES FROM 14-64 %

CAUSES INCLUDE
- DECREASED ABILITY TO CONCENTRATE URINE
- INABILITY TO
  - REGULATE FLUID VOLUME
  - REGULATE SODIUM CONCENTRATIONS
  - HANDLE ACID LOADS
  - EXCRETE POTASSIUM AND MEDICATIONS
  - BLEEDING
  - ARRHYTHMIAS
ADDITIONAL CAUSES OF MORBIDITY

INCLUDE:

- ANEMIA
- PERICARDITIS
- NEUROPATHY
- CLOTTED VASCULAR ACCESS
- INFECTION
THANK YOU