DRUG-INDUCED DISEASE: Making the Case for MTM FROM DIAGNOSIS TO TREATMENT Where do Drugs Fit in Differentials? "*Primum non nocere*"

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OUTLINE DRUG-INDUCED DISEASE (DID)

- Rationale – Objectives, Statistics, Examples
- Disease Category
  - Definition, Epidemiology, Mechanism
  - Causative Agents, Clinical Presentation, Management
- Verifying Drug Induced Disease
- Combinations of Medications Leading to DID

OBJECTIVES OF THE PRESENTATION
Drug Induced Disease (DID)

1. Identify an approach to incorporating DID w/i the differential.
2. Identify the components of the history required to rule in/out a drug causation.
3. Identify the laboratory tests required to rule in/out as drug-induced causation.
4. Identify risk factors for high probability DID causation.

THE STATISTICS

- DID death rates ↑2003 - 2007 among men and women of all race/ethnicities, with the exception of Hispanics, and rates are highest among non-Hispanic whites. Prescription drug abuse now kills more persons than illicit drugs, a reversal of the situation 15–20 years ago
- 12.4 cases / 100K

RECENT EXAMPLES OF DID

Drug-Induced Disease

- **Liver toxicity secondary to Acetaminophen**
- **MI and stroke secondary to COX-2 Inhibitors**
- **Erectile dysfunction secondary to NSAIDs**
- **Hepatic injury secondary to bromfenac, troglitazone**
- **CHF secondary to Rosiglitazone**
- **Heart, kidney, breathing problems in premature infants secondary to Kaletra**

Medications Removed From the Market

- **Life threatening cardiac arrhythmias secondary to terfenadine, astemazole, cisapride**
- **Tardive dyskinesia secondary to metoclopramide**
- **Heart valve disorder secondary to fenfluramine and dexfenfluramine**

DRUG-INDUCED DISEASES (DID) BY DISEASE STATE

- Allergic/Immunologic
- Neurological
- Psychiatric
- Respiratory
- Cardiovascular
- Endocrine
- Gastrointestinal
- Kidney, Fluids, Electrolytes
- Hematological
- Bone, Joint, Muscle

ALLERGIC / IMMUNOLOGIC DISEASES

- Drug allergy and Pseudoallergy
- SLE-like Syndrome
- Photosensitivity
- Alopecia and Hirsutism
- Oral Manifestations of Systemic Drugs

- **Causative Agents: All Rx**
  - **Penicillins, Cephalosporins, Sulfa, Tetracyclines, Aromatic anticonvulsants, ACEI, Salicylates, Radiocontrast media**
- **Clinical Presentation / Differential**
  1. Type I: anaphylaxis/urticaria/angioedema – IgE – min to 2hr after 2nd exposure – may be delayed 48 hr
  2. Type II: cytopenias/vasculities – IgG or IgM – 7-21 days
  3. Type III: serum sickness/ vasculities/ rash/ urticaria/glomerulonephritis /interstitial nephritis/erythema multiformes /Stevens-Johnson – IgG or IgM – 5-21 days
  4. Type IV: contact dermitis / exanthematous rxns / rash / bullous, pustular eruptions / Stevens-Johnson / toxic epidermal necrolysis / interstitial pneumonitis / granulomatous hepatitis – Sensitized T lymphocytes – 24-48hr
- **Management**
  - Prevention
  - D/C Rx
  - Epinephrine
  - Supportive (nutrition, pain, fluids)

Drug Allergy (Drug Hypersensitivity) & Pseudoallergy

Definition

- Adverse drug reactions mediated by the immune system
- Drug is an antigen that elicits antibodies or sensitized T lymphocytes
- Pseudoallergy describes allergic-like reactions

Epidemiology

- Hypersensitivity, intolerance, pseudoallergy comprise 25% of all ADR
- Hypersensitivity 6-10% of ADR
- Drug induced anaphylaxis due to penicillin and radiocontrast media
- ED admissions for angioedemia d/t ACEI

Mechanism

- **Drug potential to serve as an antigen dependent on:**
  - Molecular weight > 4K Da (erythropoietin, insulin, biologic agents)
  - Drugs containing foreign proteins or nonhuman origin (streptokinase, beef/pork insulin, monoclonal antibodies, l-asparaginase)
  - Drug/metabolite must bind to tissue or cell protein = hapten (penicillins, sulfonamides

Causative Agents

- Procainamide
- Hydralazine
- Isoniazid
- Methyldopa
- Quinidine
- Chlorpromazine

Clinical Presentation

- 3wks – 2yr w/1-2 symptoms
- Prodromal S/S of arthralgia, arthritis
- Constitutional S/S = fever, malaise, musculoskeletal (myalgia, arthralgia, arthritis), serositis pleurisy, pericarditis, pleural effusion, pulmonary infiltrate), hepatomegaly, splenomegaly, skin

Differential

- +ANA, lupus erythematosus cells, antihistone antibodies, lack of antibodies to DNA
- Some drugs cause +ANA w/o S/S
- -ANA for quinidine or minocycline and S/S
- Drug-induced SLE less likely to have CNS or kidney than idiopathic SLE
- Criteria for Drug-Induce SLE:
  - Adequate exposure
  - Temporal association
  - +ANA + 1 clinical symptom
  - Remission upon D/C of drug

Management

- D/C drug
- Rx ASA or NSAID for pain
- Rx low dose steroids for pleurisy
- Rx Hydroxychloroquine 200mg BID for skin and joint symptoms

SLE-like Syndrome

Definition

Autoimmune disease involving musculoskeletal, skin, kidneys and CNS

Epidemiology

- 15K-20K cases / year
- 30-50K people have drug induced SLE in US
- 5-10% of cases of SLE are drug induced

Mechanism

- Alterations in immunologic pathways or drug metabolism
- Molecular mimecry – Rx like a nucleic acid (hydralazine – adenosine)
- Nucleic acid alterations
- Immunoregulatory alterations (Procainamide – T lymphocytes)
- Interference in complement pathway (Isoniazid)
- Predisposing generics (family Hx arthritis, myalgia, Rx rxn, pleuritic pain, epilepsy, leukopenia)

- Causative Agents
  - Diuretics and Phenothiazines
  - NSAIDs
  - Antibacterials
  - Psoralens
  - Photosensitizing agents

- Clinical Presentation / Differential
  - Photosensitivity -- similar to sunburn
  - Phototoxic
  - Photosensitivity – areas exposed to sun
  - Phototoxic – w/i 30min-hrs, sunburn, erythema, pain
    - NSAIDs, Coal tar, tetracyclines, sulfonamides, fluoroquinolones, phenothiazines, thiazides, amiodarone
  - Photoallergic – 24-48hr to 14 days w/papulovesicular, intensely pruritic, eczematous rash
    - Similar to contact dermatitis
    - Tetracyclines, sulfonamides, phenothiazines, antihistamines

- Management
  - Phototoxic: treat as sunburn
  - Photoallergic:
    - Rx antihistamines
    - Rx Prednisolone 1mg/kg/day x 3-4 days
    - Rx Topical corticosteroids (Betamethasone 0.1% Cream), NSAIDs (Indomethacin 25mg TID)

Photosensitivity

Definition

Undesirable pharmacological reaction to light irradiation

Epidemiology

- Photodermatoses 11.3%
- Dermatologis treated hospital 3%

Mechanism

Photosensitivity classified as:

- **Phototoxic (most common) – drug acts as chromophore on first exposure, dose related**
- **Photoallergy – immunologic hapten**

NEUROLOGICAL DISEASES

- Seizures
- Stroke
- Movement Disorders
- Peripheral neuropathy
- Visual Disturbances
- Delirium
- Sleep Disorders
- Cognitive Disorders

- Causative Agents
  - Drugs of abuse, antidepressants, antipsychotics, antidiabetics, antibiotics, antihistamines, antineoplastics, salicylates, NSAIDs, cyclosporin
- Clinical Presentation / Differential
  - DID are generalized tonic-clonic
    - Rx cause seizures at usual dose or subratherapeutic dose ?
    - Seizures d/t supratherapeutic dose: Lidocaine, tricyclic antidepressants, INH, theophylline
  - Hx: assess previous neuro disease and conditions that may cause seizures
  - Medication Hx: Prescription Rx, OTC, herbal, illicit drug use
    - Evaluate temporal relation b/t initiation of Rx, dose adjustments, or D/C Rx
    - CBC, LFT, serum chem, urine drug screen, serum drug conc
    - EEG can't differentiate DID vs. idiopathic
    - Cyclosporin seizure: high-resolution MRI for evaluation of structural damage to CNS and possibility of opportunistic infection
    - Antiepileptic drugs: paradoxical ↑ frequency soon after initiation of Rx and often accompanied by encephalopathy, asterixis, urinary incontinence, fever, exacerbation of other existing neuro conditions – serum drug concentrations w/i normal range
  - Risk factors
    - Patient-specific: meningitis; metabolic derangements →↓ or ↑serum Na, Ca, Phos, glucose; hypoalbuminemia; kidney/liver dysfunction; genetic inherited low seizure threshold
    - Drug specific: drug-drug interactions, drugs that cross the blood-brain barrier
- Management
  - Dose reduction or D/C Rx usually resolves w/i 7-10 days
  - Rx Benzodiazepines and barbiturates + short term anticonvulsant
  - Poisoning or overdose – usual management

SEIZURES

Definition

- OTC, herbal and Rx drugs
- Rx associated w/increase in frequency or severity in epilepsy
- Rx also cause seizures in healthy individuals

Epidemiology

- 8% of US pop experience 1 seizure during lifetime
- 120 / 100K new onset / year
- DID depends on drug
- 1.7% of patients presenting to a neurology clinic
- 0.08% of patients in Boston Collaborative Surveillance Program
- SF PCC incidence of DID:
  - 29% d/t cyclic antidepressants
  - 29% d/t cocaine, stimulants
  - 7% d/t diphenhydramine and other antihistamines
  - 5% d/t theophylline
  - 5% d/t isoniazid

Mechanism

- Inhibit dopamine-2, histamine-1, adrenergic α1-receptors (antipsychotics)
- Influence neurosteroid sex hormones (progesterone, allopregnanolone, pregnenolone) -- antipsychotics
- Pharmacologic kindling = rept admin of subconvulsive doses of CNS excitatory agent – antipsychotics, cocaine, amphetamines
- Inhibit GABA (antibiotics)
- Deplete glucose in brain (NSAIDs)

- Causative Agents
  - Embolic: heroin, cocaine, methylphenidate, tamoxifen
  - Vasoconstriction: Cocaine, amphetamine, SSRI, sumatriptan
  - Acute HTN: Amphetamines, cocaine, alcohol, cigarettes
  - Vasculitis: cocaine, heroin, amphetamines
  - Direct vascular damage: NSAIDs, cisplatin
  - Clotting derangements: Cocaine, cigarette smoking
  - Orthostatic hypotension: atypical antipsychotics

- Clinical Presentation / Differential
  - Temporal relation w/drugs of abuse or drug screens
  - CT scan (anatomical location) to differentiate ischemic vs. hemorrhagic stroke
  - Same PE as idiopathic stroke
    - Common: Abrupt onset of neurological deficits
    - Hemorrhagic: Headache, impaired level of consciousness, N&V, extreme HBP
    - Subarachnoid hemorrhage: Sudden new severe headache
  - Exclude other causes: seizure, migraine, metabolic encephalopathy, tumor, abscess, encephalitis, meningitis, post MI, psychiatric S/S, trauma, genetics
  - May occur at any time during Tx w/causative agent
  - Risk factors: Hx of HBP, risk factors for stroke →higher risk of DID (HBP, ↑cholesterol, glucose intolerance, smoking, LVH)

- Management
  - Acute:
    - rt-PA for acute ischemic stroke w/i 3-4.5 hr.
    - Tx fever and hyperglycemia as they exacerbate cerebral ischemia and worsen neurological outcome
    - Rx Antihypertensive drugs IV (labetalol, nicardipine)
  - After acute phase:
    - Risk factor management – ASA, clopidogrel, ticlodipine, warfarin
    - Aggressive management of hyperlipidemia, hypertension, diabetes

STROKE

Definition

- Sudden onset of focal neurological deficit. Two types: ischemic and hemorrhagic. DID implicated in both types.

Epidemiology

- Most common non-DID stroke is ischemic (85%) and 65% of these are atherothrombotic
- Adults < 50 y/o DID is 15-38% of ischemic strokes

Mechanism DID

- Cerebral embolism
- Vasoconstriction / vasospasm
- Acute HTN
- Vasculitis
- Direct vascular damage
- Orthostatic hypotension

- **Causative Agents**
  - **Insomnia**: SSRIs, Venlafaxine, Bupropion, lovastatin, corticosteroids, Antiparkinsons, HRT (hot flashes)
  - **Daytime sleepiness**: MAOI, SSRIs, Anticonvulsants
  - **Nightmares/insomnia**: β antagonists (propranolol, timolol), α2 agonists (clonidine, methyldopa)
  - **Inability to maintain sleep/insomnia**: Alcohol, stimulants (theophylline, caffeine, cocaine, methylphenidate)
- **Clinical Presentation / Differential**
  - **S/S**: inability to fall asleep, maintain sleep, not rested, daytime sleepiness, poor cognition, lack of concentration
  - **P/E**: Hx, Rx history (emphasize Rx affecting neurotransmitters, frequency and timing of Rx, recent Rx D/C), physical, psychiatric assessment
  - **Risk factors**: female, increasing age, CNS Rx, combo of agents w/CNS effects, drug interactions)
- **Management**
  - D/C offending agent, S/S disappear relative to t1/2
  - Can't D/C offending agent:
    - Reduce dose (short-term benzodiazepine or hypnotic Rx)
    - Administer early in day
    - Sleep hygiene
    - Monitor symptoms

SLEEP DISORDERS

Definition

- Insomnia reported as difficulty in falling asleep, not rested, daytime sleepiness
- Effects immediate upon initiating Rx, or during withdrawal
- Drugs may exacerbate existing sleep disorders (sleep apnea)
- Effects of Rx on sleep identified and characterized by subjective data, PSG (polysomnography), Multiple Sleep Latency Test, and objective performance data – PSG doesn't always correlate with subjective complaints

Epidemiology

- Insomnia reported in 1/3 of US adults
- DID: 1%-55%
- Greater in females and aged

Mechanism

- Sedative effects of Rx for insomnia carry over into daytime
- Desired effects of Rx may affect receptor sites responsible for sleep
- Withdrawal effects of Rx may lead to sleep disturbance

PSYCHIATRIC DISEASES

- Depression
- Anxiety
- Psychosis

- **Causative Agents**
  - Anti-infectives (1.6-2%), cardiovascular (1.1-14%), CNS (3-40%), dermatological (1-5.5%), hormonal (1.3-54%), immunologic (0-33%), chemotherapeutic (0-33%)
- **Clinical Presentation / Differential**
  - Same as S/S endogenous depression
  - Suicidal ideation, psychotic S/S w/INFα and corticosteroids
  - Onset of depression in 1st weeks
  - GnRH agonists: depression at time of hypogonadal state
    - In vitro fertilization – S/S transient, less severe
    - Tx endometriosis – S/S persistent, severe
  - Risk factors: female, family Hx, childhood abuse, anxiety, sleep disorders, neurological disorders, drug dosage
- **Management**
  - Education and support
  - Psychotherapy – benefit in DID is unclear
  - S/S severe, persistent: D/C agent, antidepressant
  - Cardiac, OC: Switch to Rx w/lower risk in same category
  - Immunologic Rx: D/C INF (or change to INFα 2a), or SSRI (Citalopram)
  - GnRH: SSRI (Sertraline)
  - Steroids: Li, SSRI, ECT
  - Antiepileptic Rx: SSRI (but may be epileptogenic)

DEPRESSION

Definition

- **Biological illness w/NKA etiology**
- **DID similar to endogenous depression w/similar risks**
- **DSM-IV: prominent, persistent disturbance of mood during use or w/i 1 mo. of intoxication or W/D of Rx**
- **Presence of 3 characteristics severe enough to cause disruption in daily living (symptom like depressed mood, cluster of depressive symptoms, or as diagnostic entity)**

Epidemiology

- **17% lifetime prevalence**
- **Higher rate in chronic illness**
- **Isotretinoin (37 cases of suicide, 394 cases of depression) – onset 30 days, recovery 4.5 days**
- **Antihypertensives (ACEI, βB, CCB, anti-adrenergic—reserpine, methyldopa, clonidine, guanethidine, HCTZ) -- ↑risk**

Mechanism

- **Direct alteration of bioamine (antihypertensives)**
- **Disturb hypothalmic-pituitary-adrenal axis (digoxin, vinca alkaloids on dopamine)**
- **Hormonal changes (GnRH, OC, HRT, Tamoxifen) ↑cytokine production (INFα, β, IL2)**

- Causative Agents
  - Stimulants (caffeine, nasal decongestants, amphetamines) – more pronounced at hi dose, patients w/pre-existing primary anxiety, slow hepatic metabolism
  - SSRI (hi dose, fast withdrawal)
  - Benzodiazepine, gabapentin (fast withdrawal)
  - Drugs of abuse/toxins
  - CNS active agents, HRT, antihypertensives, antilipidemics
  - Antiinfectives, anti-inflammatory, anti-neoplastics, OTC, herbals – case reports
- Clinical Presentation / Differential
  - Significant (not situational) anxiety
    - Emotional S/S: xs fear, tension, nervousness, jittery, irritable, on-edge
    - Cognitive S/S: difficulty concentrating, blanking out, xs worries
    - Physical S/S: insomnia, restlessness, racing heart, difficulty breathing, sweating, flushing, weakness, exhaustion
    - Risk factors: SAD, GAD, PD, PTSD, OCD
    - High rates of antihypertensive drug intolerance
- Management
  - DID short-lived (days-weeks)
  - D/C causative agent or decrease dose + supportive treatment
  - Supportive treatment: reassurance, relaxation techniques, avoidance of other causative agents

ANXIETY

Definition

DID involved w/persistent, moderate to severe anxiety that impairs functioning, and if left untreated, can lead to depression or EtOH abuse

Epidemiology

- Primary anxiety disorder 2-15%
- Primary anxiety predisposes DID

Mechanism

- ↑noradrenergic outflow from locus cereleus of CNS (stimulants, yohimbine, benzodiazepine w/d)
- Drug specific mechanisms

RESPIRATORY DISEASES

- Pulmonary Fibrosis / Interstitial Pneumonitis
- Asthma / Bronchospasm

Causative Agents: Cytotoxic Rx

Clinical Presentation

- Acute Phase (pneumonitis)
  - Acute Dyspnea, Non-Productive Cough, Tachypnea Progresses hours - days
  - PE: crackles at base
  - PFT: normal, but CO diffusing capacity ↓
- Chronic Phase (most common)
  - Dyspnea on exertion, fatigue, non-productive cough slow progression over weeks – months

Differential: Known exposure to Rx

Management

- Lowered dose
- D/C Rx
- Prednisone 40-80mg/day (60-100mg/day if fibrosis)

Pulmonary Fibrosis / Interstitial Pneumonitis

Definition

- Scarring of lung parenchyma 2° chronic inflammatory process leading to restricted airway and death
- **DID – Causative agent is known**

Epidemiology / Causative Agents

- 327 cases / 100K (0.33%)
- DID – dose dependent

  Oncologic Rx
  - Bleomycin, Busulfan 4%
  - Carmustine 20-30%
  - Methotrexate 7% (Ca), 3-4% (RA)

  Non-Oncologic Rx
  - Amiodarone 10-20%
  - Gold salts (RA) 1%
  - Nitrofurantoin, sulfasalazine <1%

Mechanism

- Idiopathic pulmonary fibrosis and oxidant lung damage
- Nitrofurantoin / sulfasalazine – hypersensitivity

Causative Agents

- Aspirin
- Sulfites
- B blockers

Clinical Presentation /Differential

- S/S same as asthma/COPD
- Rx challenge in lab
- Anaphylaxis d/t Rx, then skin test, IgE test w/RAST
- AIA: >=30 y/o rhinitis, nasal congestion persistent, viral infection before rhinitis
  - P/E: nasal polyps, =< 5yrs before asthma or ASA sensitivity
  - Acute asthma w/i 3hr of Rx ASA or NSAIDs (rhinorrhea, conjunctivitis, flushing)
  - Dx: ASA PO provocation → ↓FEV1 and/or S/S
    - Nasal provocation Rx lysine-ASA →H20 discharge
    - Bronchial provocation Rx lysine-ASA
    - IV provocation Rx indomethacin or lysine-ASA
    - No in vitro test
- Sulfite: Established severe asthma S/S severe wheezing, chest tight, dyspnea
  - Confirm by challenge and Hx
- Latex: Clinical Hx + skin test and IgE anti-latex serology
  - Provocation if clinical history conflicts w/skin test
- ACEI: 1 day – 12mo after ACEI, and resolves 1-7 days after D/C ACEI
  - Differential: asthma, smoking, COPD, postnasal drip, CHF, URI, GI reflux
  - Women (2x), African American/Asian
  - D/C ACEI and S/S resolve 1-7 days, but may be 2 wks
- BB: Non-selective but selectivity is dose dependent

Management

- Avoidance or desensitization (ASA titrated 2-3 days to clinical dosage, then QD, but full sensitivity =< 7days after D/C ASA)

Asthma / Bronchospasm

Definition

- DID – same as other causes of bronchospasm
- Risk factor – pre-existing asthma

Epidemiology

- Prevalence 5-10%
- DID – w/pre-existing asthma
  - ASA / NSAIDs 6-34%
  - Sulfites 1% (5% in steroid-dependent asthmatics)
  - Non-selective β blockers UNK
  - ACEI cough 15-39%

Mechanism

- AIA: ASA sensitivity, asthma, nasal polyps
- Sulfite-induced bronchospasm:
  - stimulation of parasympathetic receptors after SO_2
  - IgE rxn w/+skin test
  - ↓ sulfite oxidase enzyme in sulfite sensitive patients
- B blockers: Non-selective →bronchoconstriction, bronchodilatory effect compromised

CARDIOVASCULAR DISEASE

- Ischemia and MI
- Heart Failure
- Arrhythmias
- Hypertension
- Hypotension
- Valvular and Pericardial Health Disease

- Causative Agents
  - CCB, Glitazones, anti-arrhythmics, doxorubicin, NSAIDs, COX2, BB
- Clinical Presentation
  - Not different from idiopathic HF, but S/S occur gradually on initiation of Rx
- Differential
  - Temporal relation (w/i days)
  - Fluid retention: Plasma volume expands in days to S/S dyspnea
- Management
  - Aggressive diuresis and supportive care
  - Remove offending agent (recovery related to t1/2, except Doxorubicin w/onset 30 days after last dose)
  - Rx ACEI, BB, Spironolactone, Digoxin

HEART FAILURE

Definition

Idiopathic HF due to coronary artery disease (75%). DID is frequently exacerbation of HF S/S in established HF. DID w/o preexisting HF is rare.

Epidemiology

- <1% (COX2) - 26% (CCB)
- 2.2% Doxorubicin
- 17% Glitazones
- Hospital LOS = 13 days
- In-hospital mortality 15%

Mechanism

- ↓myocardial contractility (CCB, BB, antiarrhythmics, anthracyclines)
- ↑preload (glitazones, NSAIDs, COX2, corticosteroids)
- ↑afterload (sympathomimetics)

- Causative Agents
  - NSAIDs, COX2, BB, OC, MAOI, steroids adrenal/ anabolic, antidepressants, amphetamines/anorexiants, cyclosporine, darbopoietin, tacrolimus
- Clinical Presentation /Differential
  - 2-4mm Hg impact (?)
  - 2mm Hg ↓ correlates w/17% ↓ HTN prevalence, 6% ↓ risk of CHD, 15% ↓ risk of stroke/ TIA
- Management
  - D/C offending agent (2-4 wks BP nl)
  - If BP does not return to nl, then essential HTN or other secondary HTN

HYPERTENSION

Definition

- 90-95% primary HTN
- HBP d/t use, stop of drug
- DID: BP increases from baseline leading to Stage 1 or higher (>=140/90 or =<130/80 DM or kidney disease)

Epidemiology

- 28.7% of Americans
- DID incidence low, exacerbation high 3% (anabolic steroids) - 50% (Cyclosporin)

Mechanism

- SANS (cocaine, amphetamines, ephedra, antidepressants)
- Kidneys renin-angiotensin-aldosterone (NSAIDs, COX2, immunosuppressants)
- Hormonal regulation (OC, adrenal steroids)

ENDOCRINE DISEASES

- Glucose and Insulin Dysregulation
- Thyroid Disorders
- Hypothalamic, Pituitary, and Adrenal Disorders
- Weight Gain
- Temperature Dysregulation
- Sexual Dysfunction in Males
- Gynecologic Diseases

- Causative Agents
  - Hyper: Glucocorticoids, protease inhibitors, atypical antipsychotics, niacin, pentamidine, diazoxide
  - Hypo: Insulin, sulfonylureas, ethanol
  - Hypo in =< 2y/o: salicylate poisoning
- Clinical Presentation /Differential
  - Dx of DM:
    - Fasting glucose >=126 mg/dL x 2
    - S/S and random glucose >=200 mg/dL
    - >=200 mg/dL 2hr after 75g PO glucose load
    - DID: hours – months after Rx
  - Rule out other causes
    - Physiologic stress – surgery, fever, trauma
    - Cushing's d/t exogenous glucocorticoids or endogenous overproduction of glucocorticoids
    - Intentional self-admin of insulin or sulfonylurea, intentional overdose
  - Temporal relation between Rx and S/S
    - Rx withdrawal and rechallenge
- Management
  - D/C Rx with return to baseline dependent on t1/2 of Rx
    - Return to baseline w/I days (common)
    - Longer if Rx induced hyperglycemia via weight gain or peripheral insulin resistance (atypical antipsychotics, protease inhibitors, corticosteroids)
  - Reduce dose for corticosteroids (dose-dependent effect)
  - Change Rx to another Rx w/i same class (e.g., Olanzapine to Ziprasidone, protease inhibitor to abacavir)
  - Non-reversible when permanent destruction pancreatic β cells (pentamidine)

GLUCOSE & INSULIN DYSREGULATION

Definition

Hyper or hypo DID d/t alteration of insulin secretion and sensitivity, change in gluconeogenesis, direct cytotoxic on pancreatic β cells

Epidemiology

- Unknown – lack of data, under-reporting, dose/ frequency /duration
- Varies w/i class
  - More common w/Olanzapine, Clozapine
  - More common w/long acting sulfonylureas

Mechanisms

- Alterations of insulin secretion
- Changes in insulin sensitivity directly or indirectly promoting weight gain
- Changes in gluconeogenesis
- Contributing factor unmasking preexisting DM
- Rx induced pancreatitis

Causative Agents

- Highly probable: Amiodarone, Lithium, iodinated compounds
- Probable: Interferon α-2a, 2b; Interferon β-1a, Bexarotene
- Possible: Aldeslukin, Aminoglutethimide, Aripiprazole, Quetiapine, Sertraline, Stavudine, Kelp

Clinical Presentation / Differentiation

- Dose-response relation not identified
- Exclude primary causes
  - Hyper: Graves, toxic multinodular goiter, subacute thyroiditis, toxic adenoma, thyrotoxicosis factitia
  - Hypo: Hashimoto's, dyshormonogenesis, I deficiency, infiltrative Dz (amyloidosis, sarcoidosis)
- Risk factors: age, sex, TH status, I status, nutritional status, comorbidities (thyroid Dz, diabetes, RA, pernicious anemia)
- Some w/new onset HF, AF, angina
- Elderly w/unexplained weight loss requires evaluation of malignancies
- Hyper:
  - Early S/S of constipation, fatigue, weight gain, dry skin may be incorrectly attributed to normal process of aging
  - TSH suppressed or undetectable + elevated FT4 = hyper
  - TSH suppressed or undetectable + normal FT4 = subclinical hyper
  - DID: total T3 and FT4
  - Amiodarone induced hyperthyroidism: TSH suppressed + FT4 elevated
    - Type I I uptake normal
    - Type II I uptake reduced
- Hypo:
  - TSH elevated + low FT4 = overt hypothyroidism
  - TSH elevated + normal FT4 = subclinical hypothyroidism
- R/O Euthyroid sick syndrome: altered thyroid hormone metabolism due to fasting, malnutrition, infection, cancer, surgery, chronic Dz (cardiac, pulmonary, renal, hepatic), acute psychiatric illness, metabolic disorders (DM)

Management

- D/C Rx or rechallenge in months
- Amiodarone induced hyperthyroidism: Methimazole or PTU

THYROID DISORDERS

Definition

Thyroid hormone regulates metabolism, and DID affects TH synthesis ,release, or function.

Epidemiology

- Hypo: 1.5-2% in women and 0.2% in males
  - 3.5 / 1K women, 0.6 /1K males
  - 14 / 1K women 75-80 y/o
  - Subclinical hypothyroidism 20% of patients over 60 y/o
- Hyper:
  - 0.8 / 1K women
  - Subclinical hyperthyroidism 2-16%
- DID: <1% - 34% (Li)

Mechanism

- Changes in auto-regulation (Wolff-Chaikoff block)
- Inflammatory / autoimmune thyroiditis
- De novo development of thyroid antibodies

- **Causative Agents**
  - Thiazide diuretics, β blockers, antipsychotics, antidepressants
- **Clinical Presentation / Differential**
  - Same as SD d/t other causes
  - Hx: past medical problems, prescription Rx and OTC
  - ED: International Index of Erectile Function or Brief Sexual Function Inventory at baseline and after intervention
  - ↓libido: 2 serial measurements of serum testosterone in AM
  - Ejaculatory dysfunction: 2 semen samples on 2 separate days, preceded by 3 days of sexual abstinence
  - Retrograde ejaculation: post-ejaculation urine evaluated for sperm
  - Risk factors for DID: age > 40, smoking, excess EtOH, CAD, HBP, DM, spinal cord injury, stroke, cancer
- **Management**
  - D/C causative agent
  - Dose reduction
  - Rx another Rx is discouraged
  - Erectile dysfunction: Sildenafil, alprostadil
  - Ejaculation disorders: Imipramine 25-50mg QD x 7 days prior to ejaculation or Pseudoephedrine 60mg QID x 3 days, or Sertraline 50mg QD x 1-2 weeks

SEXUAL DYSFUNCTION (SD) IN MALES

Definition

- Disorders of libido (↑↓sex drive)
- Erectile dysfunction (penile impotence)
- Ejaculatory disorders (premature, anejaculation, ↓volume, retrograde)
- Priapism (Prolonged, painful erection)
- infertility

Epidemiology

- 25% of erectile dysfunction may be DID
- More common in men Rx antihypertensives, oral hypoglycemics, vasodilators, or cardiac meds
- 51% of men age 40-70 (Mass Male Aging Study)
- Patient factors: age, dose, combo of Rx causing SD, concomitant Dz

Mechanisms

- Disorders of Libido: LHRH or GnRH→LH→testosterone
- Disorders of penile erection: inadequate arterial blood flow < venous outflow (antihypertensives, diuretics)
- Disorders of erectile dysfunction: mediated by acetylcholine so receptor antagonists →anticholinergic effects
- Ejaculation disorders: mediated by NE so α adrenergic antagonists block NE (terazosin)
- ↓volume: Rx interfere w/production of seminal fluids (finasteride)

GASTROINTESTINAL (GI) DISEASES

- Upper GI Ulceration
- Diarrhea and Constipation
- Hepatic and Cholestatic Diseases
- Pancreatitis
- Nausea, Vomiting, and Anorexia

- **Causative Agents**
  - ASA, NSAIDs, KCl, corticosteroids, doxycycline, $FeSO_4$, bisphosphonates
- **Clinical Presentation / Differential**
  - Many patients asymptomatic so hard to define temporal relation
  - Endoscopy indicates NSAID ulcer w/i 8 weeks
  - Bleeding presents as hematemesis or melena
  - Emesis, dysphagia, weight loss precede acute bleed
  - Possible POB if bloody emesis, bloody/black tarry stools, or abdominal tenderness
- **Management**
  - D/C offending agent
  - ASA/NSAIDs: Eradicate HP, heal ulcer w/PPI, misoprostol
  - Bisphosphonates, KCl, Tetracyclines, Quinidine: Consider other Rx, xs H_2O, don't take w/meals, avodi recumbent position for 1hr

UPPER GI ULCERATION

Definition

- Ulcerative or inflammatory lesions of the esophagus, stomach, or duodenum
- Results in perforation, obstruction, or bleeding (POB)
- Exception: ↑risk of bleeding (heparin, warfarin, clopidogrel) are not primary causes of ulceration

Epidemiology

- Ulcer = lesion of >=3mm
- 2.5% ASA dose < 100mg
- 10-15% ASA for RA will have gastric ulcer after 1 month (not reduced w/enteric-coated ASA)
- 10-15% COX1 NSAIDs or 1.3-2.2/1K patient years
- 5-8% COX2 NSAIDs
- POB: 1/210 patients > 45 y/o
- 19% KCl (reported as high as 67%)
- 0.4% - 1.5% Bisphosphonates (alendronate endoscopic trials report 12-14%, but same as placebo for risendronate)

Mechanism

- Altered PG defense mechanisms (ASA,NSAIDs)
- Direct topical irritation (bisphosphonates)
- Low pH leading to erosion (doxycycline, $FeSO_4$)

KIDNEY / FLUIDS / ELECTROLYTE DISORDERS

- Acute Renal Diseases
- Chronic Kidney Disease
- Syndrome of Inappropriate Antidiuretic Hormone Secretion / Diabetes Insipidus
- Acid-Base Disorders

- **Causative Agents**
  - Hemodynamically mediated: NSAIDs, ACEI, ARB, Cyclosporin, Tacrolimus
  - Acute interstitial nephritis: NSAIDs, β-lactam antibiotics, Rifampin, diuretics, H2RA, PPI, Erythromycin, Ciprofloxacin, Allopurinol, Phenytoin, Li, Valproic Acid
  - Acute Tubular Necrosis: Aminoglycosides, Amphotericin B, Radiocontrast media
  - Nephrolithiasis: Sulfonamides, Allopurinol, Indinivir, Foscarnet, Acyclovir, MTX
  - Glomerulonephritis: Au, Penicillamines, NSAIDs, Phenytoin, Rifampin, Li, Allopurinol, Hydralazine, PTU
- **Clinical Presentation / Differential**
  - Acute hypovolemic condition (gastroenteritis) associated w/↑SCr – ACEI, ARB w/i 2 weeks
  - Lab findings of prerenal azotemia w/o S/S of fulminate uremia
  - Risk factors: Other causes of prerenal azotemia – hypovolemia (xs diuresis, vomiting, diarrhea), CHF, cirrhosis, sepsis
- **Management**
  - Drug dependent
  - Necessary only if ↑SCr >30% of baseline
  - Usually supportive w/aggressive hydration
  - Dialysis only indicated if renal insufficiency w/signs of uremia or recalcitrant hyperkalemia

ACUTE RENAL FAILURE (ARF)

Definition

- Increase in SCr of 25-30% above baseline
- Kidneys receive 25% of cardiac output and renal hemodynamics may be altered by drugs

Epidemiology

- 5% of hospitalized patients and 20% of cases are caused by Rx
- 6.7% of drug-related complications in adverse events in hospitalized patients

Mechanism

- Renal hemodynamics alterations leading to ↓renal perfusion
- Direct toxicity to renal tubule (acute tubular necrosis)
- Tubulointerstitial inflammation 2nd allergic rxn (acute interstitial nephritis)
- Precipitation of Rx crystals leading to obstruction (nephrolithiasis)
- Immune mediated rxn resulting in damage to glomerulus (glomerulonephritis)

- **Causative Agents**
  - Cyclosporin/Tacrolimus, combination analgesics (Rx>1yr), Li
  - Chinese herbals (aristolochic acid)
  - Causative agents of ARF
- **Clinical Presentation / Differential**
  - Non-specific S/S attributed to RF
  - Stages of CKD: 1 (GFR>90), 2 (GFR=60-89+HTN), 3 (GFR=30-59+Anemia), 4 (GFR15-29+Neuropathy), 5 (GFR<15 or dialysis)
  - Cyclosporin/Tacrolimus: 6-12mo. after initiation of Rx; ↑BUN/SCr + hypertension, S/S same as CKD
  - Lithium: Insidious ↑SCr/BUN x 10+ yrs.; HTN and proteinuria; ↓renal function mild (CC>50ml/min)
  - Analgesics: Insidious ↑BUN/SCr w/more than ½ of kidney function lost before elevation; non-specific S/S; use QD >1yr; CT scan w/o contrast media reveals ↓bilateral renal mass, bumpy contours of kidney, and papillary calcifications
  - Chinese Herbs: Non-specific S/S, but anemia more pronounced based on stage; proteinuria and glycosuria present; kidney size ↓, biopsy reveals extensive interstitial fibrosis; urothelial lesions or urothelial transitional cell ca
- **Management**
  - Supportive
  - Cyclosporin/Tacrolimus: No Tx; Substitute may slow rate of loss of RF; weigh benefits of continued immunosuppressants
  - Lithium: D/C benefits are controversial
  - Analgesics: D/C to prevent progression to ESRD

CHRONIC RENAL FAILURE (CRF, CKD)

Definition

- Chronic condition in renal function characterized by GFR < 60 ml/min/1.73 m2, while kidney failure characterized by GFR<15 ml/min/1.73 m2

Epidemiology

- Drug specific
- Immunosuppressants (Cyclosporin, Tacrolimus) 18%
- Li polyuria 2-37%
- Analgesics 0.8-9%
- Gold IV 2-20%
- Penicillamine 2-20%

Mechanism

- Immunosuppressants: Direct vascular and tubular toxicity manifested as chronic tubulo-interstitial nephritis (fibrosis in striped pattern)
- Li: ↓intracellular cAMP or ↓H2O transport in cortical collecting duct manifested as glomerulosclerosis, widespread tubular atrophy
- Analgesics: Papillary necrosis associated w/calcification

HEMATOLOGICAL DISORDERS

- Thrombocytopenia
- Thromboembolic Diseases
- Neutropenia and Agranulocytosis
- Anemia

- **Causative Agents**
  - Hemolytic:
    - Autoimmune – methyldopa, procainamide, levodopa
    - Immune complexes (neoantigens) activate complement – quinidine
    - Direct covalent adsorption to cell membrane -- Penicillins, Cephalosporins, Tetracyclines
    - Protein adsorption (b9) – Cephalosporins
    - Multiple mechanisms – autoantibodies and Rx antibodies – NSAIDs, HCTZ
    - Pure red cell aplasia(rare) – severe normochromic, normocytic associated w/reticulocytopenia (Azathiopurine, Epoetin, INH, Phenytoin)
    - cancer chemo, Carbamazepine, H2RA, INH, Methyldopa, Primaquin, Rifampin (12-24%), Sulfonamides,
  - Aplastic: Acetazolamide, Captopril, Carbamazepine, Chloramphenicol, Felbamate, Furosemide, Au, NSAIDs, Phenytoin, Sulfonamides, Ticlodipine
- **Clinical Presentation / Differential**
  - Same as other anemias
  - DID hemolytic takes weeks, about 1 mo. for aplastic
  - Hx for meds w/i last 6 months
  - Differential: Fe, B12, folic acid deficiencies; Dz related BM suppression; EtOH; acute/chronic blood loss,
  - Hemolytic: direct Coomb's test
  - Aplastic: BM biopsy
- **Management**
  - Depends on type of anemia and exact cause
  - D/C Rx and spontaneous resolution

ANEMIA

Definition

- Reduction of hemoglobin below normal
- Normal varies w/sex, age, and altitude (12.3-15.3g/dL women, and 14-17.4g/dL in men)
- Anemia a symptom of disease requiring etiology

Epidemiology

- Least common DID blood dyscrasia
- Hemolytic anemia 1.1-1.6/M) > aplastic anemia (0.5-0.7/M)
- NSAIDs 3.1%

Mechanism

- Microcytic (MCV<80mcm3): Fe deficiency (ASA, NSAIDs, COX2)
- Normocytic (MCV 80-100mcm3): Acute blood loss, ↓erythropoietin, hemolysis, BM failure (Chloramphenicol)
- Macrocytic (MCV>100mcm3):
  - **Megaloblastic**: d/t disorders of DNA synthesis but normal RNA related to ↓FA and B12 (MTX, antimetabolites,INH)
  - **Non-megaloblastic**: EtOH, liver Dz, NTG, Sulfonamides

BONE / JOINT / MUSCLE DISEASES

- Osteoporosis and Osteomalacia
- Gout and Hyperuricemia
- Myopathies

Osteoporosis / Osteomalacia

- **Causative Agents**
  - Osteoporosis: cancer chemotherapy in young; heparin long-term in pregnant women; chronic, systemic glucocorticoids or androgen deprivation in prostate ca.
  - Osteonecrosis: glucocorticoids (=<3%), cancer chemotherapy
- **Clinical Presentation / Differential**
  - Osteoporosis:
    - Same as osteoporosis from other causes
    - Consider when Rx causative agent + osteoporosis
    - Glucocorticoids: first 6-12 mo.; vertebral Fx
    - Differential: endocrine, GI, nutritional, BM, connective tissue, genetic, renal disease
  - Osteonecrosis:
    - Most common at femoral head
    - S/S is pain at rest in groin, thighs, buttocks and 1/3 have pain at night
- **Management**
  - D/C offending drug or reduce dose
  - Men: Bisphosphonates are DOC
    - Antiresorptive Rx + lifestyle modification + prevention (avoid tobacco)
    - Glucocorticoids: T-score < -1.0
  - Women: Bisphosphonates or Raloxifene

Definition

- Osteoporosis: skeletal disorder characterized by ↓bone strength and fractures – BMD>=2.5
- Osteomalacia: pathologic loss of mineralized bone associated w/low blood conc. of Ca/P leading to ↓bone strength and fractures, bone pain, and myopathy – (Vit D↓)
- Osteonecrosis: death of bone and BM
- DID: specific Rx associated w/osteoporosis in population in which condition rarely occurs

Epidemiology

- Women mostly primary osteoporosis
- Men 30-60% secondary osteoporosis

Mechanism

- Osteoporosis DID:
  - Osteoclast activation/↑bone turnover
  - Suppression of osteoblastic activity
  - Inhibition of mineralization

- **Causative Agents**
  - EtOH
  - Ethambutol, Pyrazinamide
  - Diuretics
  - Nicotinic acid
  - Cyclosporin
  - Cytoxic agents
  - Salicylates
  - Levodopa
- **Clinical Presentation / Differential**
  - Pain, swelling, and erythema involving 1 or a few joints
  - Self-limiting 5-10 days w/o Tx
  - Asymptomatic b/w attacks (diff arthritis)
  - 4^{th}-6^{th} decade in men; 6^{th}-8^{th} decade in women
  - Dx: (1) hyperuricemia, (2) Hx acute attacks of arthritis w/asymptomatic periods, (3) ability of colchicine to abort an attack
  - Differential: pseudogout d/t Ca pyrophosphate, septic arthritis, cellulitis, fractures, palindromic rheumatism
- **Management**
  - Asymptomatic hyperuricemia – no Tx
  - Tx if > 4 attacks/year Rx NSAIDs
  - D/C offending agent is risk/benefit analysis
  - Prophylaxis: Colchicine 0.6mg BID – if breakthrough Rx Allopurinol
  - Cytotoxic agents: reduce dose 25% + Allopurinol

Gout & Hyperuricemia

Definition

- Inflammatory disease induced by urate crystals that precipitate in joints and soft tissue
- DID alter urate excretion or ↑uric acid production predisposing patients to hyperuricemia w/ or w/o gout

Epidemiology

- 1% of general population
- More prevalent in HTN
- Cyclosporin and Pyrazinamide > diuretics

Mechanism

- Interference w/uric acid excretion leading to accumulation in serum
- Anti-tumor Rx cause cell death leading to ↑uric acid
- Allopurinol and Probenecid may precipitate gout in 1^{st} several months d/t fluctuations in uric acid
- Patients w/adherence problems may experience fluctuations in uric acid

SUMMARY POINTS

- Medication history must be exhaustive, include OTC and herbals
- Question for temporal elements of initiation or rapid withdrawal of possible offending agents and onset of signs and symptoms
- DID more common as exacerbations in patients w/primary disease

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