OBJECTIVES

• Discuss pharmacotherapeutic objectives from the case-based presentation.
• Review clinically relevant therapeutic information from recent clinical trials and updated guidelines.
• Summarize up-to-date therapeutic concepts in the management of common primary care diseases.

CASE

• 83 y/o male with acute decompensated HF with bilateral pleural effusions
• COPD, CKD, HFpEF, HTN, DM, CAD w DES
• ASA 325 mg/d; Furosemide 40 mg 2xd, Clopidogrel; Isosorbide mononitrate; Metoprolol XL 100 mg/d; Simvastatin 40 mg/d
• BNP 959 pg/mL
• Cr 1.5, eGFR 35

• Diuretic therapy
  – Furosemide 40 mg IV without increase in UO
  – Furosemide 80 mg IV produced diuresis, started on continuous IV infusion with good UO
• d/c’d on Day 11
  – Furosemide 40 mg po 2xd
• 1 wk later admit with increased leg swelling & SOB
  – 3+ pedal edema
  – Bilateral pleural effusions
  – Cr 1.6; eGFR 31
  – Furosemide 40 mg IV

LOOP DIURETICS

• Site of action – receptor on luminal surface
  – Compete with Cl and block Na/K/2Cl cotransporter on thick ascending limb of loop of Henle
• >90% albumin bound – little glomerulus filtrate
• Secreted from the blood into urine
  – Organic anion transporters in proximal convoluted tubule secrete diuretic into luminal membrane
  – Secretion rate determines concentration reaching the site of action
  – Renal insufficiency reduces secretion rate

• Must attain a threshold concentration at site of action to cause a response
  – The dose to achieve a threshold concentration varies from patient to patient
• Increasing doses beyond threshold does not increase natriuresis efficiency – ceiling dose
  – Use the smallest effective dose
  – Healthy people maximal response dose
    • IV furosemide 40 mg, 1 mg bumetanide, 20 mg torsemide
**FUROSEMIDE DOSING**

- **~50% bioavailability**
  - On average 40 mg po is equivalent to 20 mg IV
- **10-100% bioavailability**
  - Unable to predict in an individual patient
- **Individualize** dose based on response when switching from IV to oral dose
  - 40 mg IV 2xd = 80 mg po 2xd at 50% bioavailability
    - May require more or less in an individual patient
  - Monitor weight, urine output, BMP

---

**LOOP DIURETICS**

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
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<tbody>
<tr>
<td>Usual dose</td>
<td>20-160 mg/d</td>
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<td>Half-life</td>
<td>0.3-3.4 h</td>
<td>0.3-1.5 h</td>
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</table>

---

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---

**LOOP DIURETICS**

Diuretic Resistance

- Post-diuretic decrease in UO
  - Duration of action of loop diuretics for several hours
- Na+ is reabsorbed when diuretic concentration falls below threshold – low Na+ excretion
  - Post-diuretic Na+ retention
  - May offset the initial natriuresis
  - May need to shorten dosage interval
  - > 1xd dosing to maintain negative Na balance

---

**LOOP DIURETICS IN ACUTE HF**

- Goal is UO of 3-5 L/d until euvoletic
- Initial IV furosemide ≥ chronic oral dose
  - Increase dose if UO stays < 3 L/d
- Diuretic resistant if little response with maximum dose of furosemide 250 mg
  - 40 mg IV furosemide = bumetanide 1 mg = torsemide 20 mg

---

**AHA 2013 DECOMPENSATED HF DIURETICS**

- Class I
  - Treat with IV loop diuretics
  - If already on taking diuretics
    - IV dose should ≥ chronic oral daily dose
    - Intermittent IV doses or continuous infusion
  - UO and s/s of congestion should be monitored
    - Adjust dose to relieve symptoms, reduce volume excess, and avoid hypotension
AHA 2013 DECOMPENSATED HF DIURETICS

- Class IIa
  - Diuresis inadequate to relieve symptoms, reasonable to intensify diuretic
  - a. Increase dose of IV loop diuretic (LOE: B); or
  - b. Add thiazide diuretic (LOE: B).

CASE

- 78 y/o female presents with medication question
  - Rivaroxaban for VTE history – wants to switch to Warfarin because of cost
  - Last dose 8 h ago
- History of 2 DVTs and PE several yrs ago
  - Has taken warfarin but was switched to rivaroxaban 6 mon ago
- PT 18.6 (12.5), BMP & CBC WNL

CASE

- 75 y/o male presents for routine f/u
  - HTN, AF, DM
- Meds:
  - Lisinopril 20 mg/d
  - Metoprolol XL 100 mg/d
  - Metformin 850 mg 2xd
  - Apixaban 2.5 mg 2xd – last dose 4 h ago
- Labs WNL including PT 13 (12.5)

DOACs AND COAG TESTS

- Each has its own effect on coag tests
  - PT, aPTT
  - Varies with reagent used & serum concentration
- PT & aPTT have low sensitivity and specificity for quantifying serum concentrations
  - Not reliable to assess concentration
  - No therapeutic range
- Do not rely on normal PT or aPTT to exclude clinically relevant anticoagulant effect

DOACs AND COAG TESTS

- Routine coag testing not recommended
  - Dabigatran
    - Increased PT, aPTT, TT, Ecarin clotting time (ECT)
      - Suggests clinically relevant anticoagulation
    - Normal PT & aPTT excludes therapeutic levels
      - Not useful for therapeutic monitoring
    - Anti-FIIa assays may be useful
      - Serum levels
DOACs AND COAG TESTS

- Rivaroxaban, Apixaban, Edoxaban
  - Elevated PT suggests clinically effective levels
    - Variability of INR to detect – sensitivity
      - Rivaroxaban 74%
      - Apixaban 56%
  - Up to 50% have a normal PT
    - Normal PT (esp. apixaban) does not exclude therapeutic levels
  - Antifactor Xa level may be used for drug quantification
    - Undetectable excludes clinically relevant levels of drug

AJM 16;129:S1-S29 Med Clin N Am 15;99:759-80

Switching DOAC to Warfarin
American Soc Hematology 2018

- Overlap DOAC & warfarin until INR is therapeutic over LMWH or UFH-bridging therapy (conditional recommendation based on very low certainty in the evidence)
- To minimize DOAC interference with the INR
  - Measure INR just before DOAC dose
  - “However, providers will need to be aware of the varying potential among DOACs to influence INR”

Blood Advances. 18;2:3257-91

CASE

- 79 y/o male with bilat maxillary sinus tenderness > 7 d and influenza 2 wks ago
- PMH: CAD, gout, HTN, LDL, OA, Sz
  - Few crackles at L base
- CBC WNL, CXR neg
- Acute sinusitis post influenza
  - Concern for secondary bacterial after influenza
  - Amoxicillin/Clavulanate 875 mg 2xd X 10d
  - See in 1 wk

1 week Later

- Wt down 7kg in 3 wks
- Neg for postnasal drainage, lungs clear
- Abd slightly tender to palpation, without masses
- CBC, CMP, UA, Lipase, abd xray, CT abd/pelvis
- Finish Augmentin
- Prilosec 20 mg/d

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DRUG-INDUCE LIVER INJURY (DILI) DRUG-INDUCED HEPATOTOX (DIH)

- Injury to liver that is associated with impaired liver function caused by exposure to a drug or another noninfectious agent
- In US
  - ~2000 cases/y of acute liver failure (>50% drugs)
  - Drugs – 2-5% hospitalized with jaundice
  - ~10% of all cases of acute hepatitis

>1000 hepatotoxic meds/supplements

DILI

- Biochemical, histological features & s/s
  - Mimic other mechanisms for acute/chronic diseases
- Need for high level of suspicion for DILI
- No “gold standard” for diagnosis
  - Diagnosis of exclusion
  - Liver biopsy does not include/exclude
  - Thorough history is important along with labs and imaging

Commonly used meds causing DILI

- Necrosis
  - Acetaminophen, ketocazole, rifampin, isoniazid, phenytoin, valproic acid, carbamazepine, venlafaxine
- Cholestasis
  - Amoxicillin/clavulanate, chlorpromazine, ACEIs, erythromycin
- Acute steatosis
  - Didanosine, valproic acid
- Mixed pattern
  - Phenytoin, TMP/SMX, nitrofurantoin, cyclosporine
- Fibrosis/cirrhosis
  - Methotrexate
- Nonalcoholic steatohepatitis
  - Amiodarone, tamoxifen, chloroquine

Amox/clav

- Most common cause of DILI
- Risk 1 out of 2500 Rx’s
- Immunoallergic & Idiosyncratic
  - May see fever, rash, arthralgias, and eosinophilia but usually not prominent
  - Considered to be primarily due to clavulanic acid from rechallenge cases

Amox/clav DIH

- Usually cholestatic – increased AP and GGT
- Sometimes see hepatocellular (AST, ALT) pattern in younger age or mixed pattern
- Often missed since may be mild and may be delayed onset
- May be severe and usually reversible
  - Rarely deaths have been reported (< 1 per estimated 4 million Rx worldwide)

Amox/clav DIH

- Onset few d to 8 wks (avg ~3 wks)
- S/S may include
  - Fatigue, low grade fever, nausea & abdominal pain, pruritus, jaundice
- Increased risk
  - Elderly, men, multiple courses
- Rechallenge with amox/clav should be avoided
  - Amox is safe except in rare instance in which the penicillin is responsible for the liver injury
MEDICATION ERRORS

“continue to be one of the most frequent causes of preventable harms in health care.”


79 y/o male with n & v, dizziness and diaphoresis with near syncpe
– HTN, CVA 6 y ago, h/o AF (warfarin allergy)
– ASA, Lisinopril
– Metoprolol XL 50 mg/d, Verapamil SR 240 mg 2xd
• 149/62, EKG in ED rate 44, PR 0.26
– Atropine 0.5 mg IV
• Taking Verapamil SR 120 mg 2xd and was switched to 240 mg ER 240 mg/d
– Misunderstood and took 240 mg ER 2xd

MEDICATION RECONCILIATION

“a process … most accurate list of all medications … including name, dosage, frequency, and route … to provide correct medications … within the health care system.”


86 y/o female with recent muscle aches & stiffness, weakness, fatigue – Ibuprofen
– PMH: CVA, HTN, LDL, CAD, AF
• Meds:
  – ASA, Dipyridamole, Enalapril, HCTZ
  – Diltiazem ER, Simvastatin 40 mg/d
• SCr 1.6 (baseline 0.8), CPK 11,045
• Had been on Simvastatin 40 mg/d (80 mg tab to take ½ tab/d)
  – Told to increase to 2 tabs/d
  – She inadvertently took 160 mg/d (max dose 40 mg/d and DDI with Diltiazem max dose 10 mg/d)

HYPOGLYCEMIA CASE

• 59 y/o female found unresponsive
  – EMS reported PG 12
  – Per home health last insulin dose last night
• DM, LDL, mild intellectual disability, MDD
  – Neuropsych testing – competent to make decisions
– Home health daily

• Collect, review, analyze meds
• Transitions of care may affect medication regimens of patients
  – Potential for reduced patient safety due to med errors and ADRs

MEDICATION RECONCILIATION

• Poor communication at “hand offs” in hospital
  – Up to 50% of all med errors
  – Up to 20% of adverse drug events
• Patient should be active participant
• Should take place whenever patient changes level of care (ED, admission, transfers, discharge) as well as in the office
  – Ensuring the med list is up to date


Mayo Clin Proc 89;89:1116-25
• Meds
  – Insulin glargine 100 units/ml – 60 units 2xd
  – Metformin 2 g/d
  – Citalopram 40 mg/d
  – Atorvastatin 80 mg/d
  – ASA 81 mg/d
• RPh f/u with home health on home meds
  – Home health draws up insulin 60 units on U-100 syringe
  – Recent insulin changes to regular insulin U-500
    • Draws up to 60 unit mark on U-100 syringe = 300 units
    – Probable cause of frequent hypoglycemia

NON U-100 INSULINS
• Short-acting regular human insulin rDNA
  – Humulin R 500 units/ml
• Rapid-acting human insulin analogs
  – Lispro – Humalog (100 & 200 units/ml)
• Long-acting human insulin analogue
  – Toujeo 300 units/ml
• Ultra long-acting human insulin analogue
  – Degludec – Tresiba; 100 & 200 units/ml

INSULIN SAFETY
• Put safeguards in place to avoid mix-ups with different strengths (e.g., U-100, 200, 300, 500)
• Educate patients and providers about differences between different strength products as related to onset, duration of action, and intended use.
• U-500 is not just a concentrated form of regular insulin
  – Onset/duration similar to premixed 70/30 insulin.

U-500 Insulin
• U-500 is FIVE times as concentrated as U-100
  – 500 units/mL instead of 100 units/mL
• Determine total daily dose of U-500 by adding units of all types of other insulins given per day
  – Divide this by 2-3 for 2-3x/d doses 30 minutes before meals
• Draw up individual doses with U-500 syringe or consider using U-500 pen
• Label order with units and volume to inject
• Stop other insulins when U-500 is started.

CASE
• 77 y/o female with acute L sided weakness, facial droop
  – LTCF resident
  – At baseline at 2400 – at 0500 noted to be mumbling, confused and slurred speech
• HTN, COPD, fibromyalgia, osteoporosis
• BP 198/129, exam consistent with CVA
• Tele-neurology – ASA and permissive HTN
• Plan: ASA + clopidogrel (3 mon) then ASA

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)
• 5170 Chinese - acute minor ischemic CVA or TIA within 24 h with high risk of recurrence
  – ASA 75 mg/d plus clopidogrel 75 mg/d for 21 d then clopidogrel continued to day 90 vs. ASA 75 mg/d for 90 d – LD were given with 1st dose
• Recurrent CVA at 90 d
  – 8.2% vs 11.7% (HR 0.68; p<0.001)
  • ARR 3.5% – NNT 29 for combo
• No difference in bleeding

NEJM 13;369:11-9
DAPT in Acute TIA and Minor Stroke

- Screened 41,561 to find 5,170
- “results cannot be generalized to most … excluded”
  - Major CVA (large intracranial vessel atherosclerosis) – lacunar infarcts in CHANCE
  - Risk for hemorrhagic transformation
  - TIA from isolated syndromes at low recurrence risk
- May not apply to non-Chinese
- Results cannot be generalized beyond 90 d

Stenting & Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis SAMMPRIS

- 451 with acute CVA or TIA from a major intracranial artery – high risk of recurrent stroke
  - ASA 325 mg/d + clopidogrel 75 mg/d for 90 d vs. meds plus stenting
- CVA or death within 30 d
  - Stopped early
  - 5.8% vs 14.7% stent group
- Aggressive medical better than stenting

SEVERE INTRACRANIAL MAJOR ARTERY ATHEROSCLEROSIS

- “typically treated with DAPT for 3 mon or longer (consistent with results of … SAMMPRIS trial”
- Accepted initial therapy of DAPT for 3 mon or longer
- Antiplatelet monotherapy vs DAPT have not been sufficiently studies but short course DAPT generally considered safe

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA. AHA/ASA

- Online 5/1/14: ASA and clopidogrel might be considered for initiation within 24 h of a minor ischemic stroke or TIA and for continuation for 90 days (Class IIb; LOE B)
- Correction 7/2014 in Stroke 14;45:2160-2236: ASA and clopidogrel might be considered for initiation within 24 h of a minor ischemic stroke or TIA and for continuation for 21 d (Class IIb; LOE. B)

2018 Guidelines for Early Management of Acute Ischemic Stroke. AHA/ASA

- Minor stroke, treatment for 21 d with DAPT (ASA & clopidogrel) begun within 24 h can be beneficial for early secondary stroke prevention for up to 90 d from symptom onset (Class IIa. LOE B-R)
  - NIHSS score ≤ 3 or high-risk TIA ABCD2 score ≥ 4
  - Generalizability in non-Asians remains to be established, a large phase III RCT in US, Canada, Europe, and Australia is ongoing

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)

- 4881 international patients with minor CVA (NIH Stroke Scale ≤ 3) or high-risk TIA
  - Within 12 h ASA + clopidogrel for 90 d vs. ASA for 90 d
- Composite of ischemic CVA, MI or death from ischemic vascular events at 90 d
  - Stopped early
  - 5% vs. 6.5% (HR 0.75, P=0.02)
  - Major bleed 0.9% vs 0.4% (HR 2.32; P=0.02)
Antiplatelet Therapy after Ischemic Stroke or TIA

- ASA plus clopidogrel reduces recurrence during 1st few wks
  - High-risk period after a TIA or ischemic stroke
- For 3 wks and then switch to to monotherapy
- Not if uncertain TIA diagnosis
  - Excluded from the trial or did not benefit
- Risk for bleed, e.g., cerebral microbleeding or h/o brain or systemic bleeding, were excluded
  - May not be appropriate

CASE

- 85 y/o female with SOB with minimal exertion
  - Admit from clinic
  - New onset SOB and fatigue
  - Scr 1.7 (1.4), K 6.2, BNP 343
  - 1 wk PTA seen in clinic for L groin pannus infection
  - TMP/SMX, Cephalexin – reviewed for DDIs – reduce atorvastatin & tolterodine (Detrol) dose
- CKD, CAD with BMS, T2DM, HTN, COPD

MEDS INCLUDE

- Cephalexin
- TMP/SMX DS 2xd
- Tolterodine ER
- HCTZ 25 mg/d
- Valsartan 160 mg/d
- Metoprolol tartrate 75 mg 2xd
- Nifedipine XL
- Isosorbide mononitrate
- Bumetanide 0.5 mg q48h
- ASA 81 mg/d
- Atorvastatin 40 mg/d
- Fenofibrate
- Allopurinol
- Pregabalin
- Insulin aspart
- Insulin detemir

ACEI/ARB ADVERSE REACTIONS

- Hyperkalemia ~3%
  - Renal dysfunction, DM, K sparing diuretics, NSAIDs, TMP/SMX, HF, elderly, KCl
  
  J Am Coll Cardiol 07;50:1959-66
  
  CMAJ 11;183:1851-8
- Increased serum creatinine (SCr)
  - Prevent autoregulation of efferent renal artery
  - Bilateral renal artery stenosis
  - NSAIDs, volume depletion, CHF, diuretics

TRIMETHOPRIM (TMP) & POTASSIUM

- Causes blockage of amiloride-sensitive Na channels in collecting duct
  - Decreases K excretion
  - Similar mechanism as amiloride (K-sparing diuretic)
- Increased risk hyperkalemia with high doses, eg for Pneumocystis jiroveci (PCP)
  - 4 DS TMP/SMX 2xd

TMP/SMX & RAAS Inhibitors

- ~ 40,000 reports of sudden death in > 66 y/o
  - If on ARB or ACEI ~1000 deaths within 7 d of TMP/SMX, amox, cipro, norflox, or nitrofurantoin
  - 3 within 14 d/1000 courses TMP/SMX vs. 1 with amox and 0 with others
  
  BMJ 18;349:g6196
- 317 > 66 y/o admitted with hyperkalemia on ACEI or ARB & an abx within 14 d
  - Almost 7X increase in admit rate if taking TMP/SMX vs. amox
  
  Arch Intern Med 10;170:1045-9
**TMP/SMX & HYPERKALEMIA**

- Monitor serum K⁺ if there is increased risk
  - High dose TMP/SMX
  - Use with ACEIs, ARBs, K-sparing diuretics, NSAIDs, & K⁺ supplements
  - Elderly, CKD, HF, DM
- Maybe use an alternative antibiotic
- Use for short a duration as possible
- Consider holding interacting drugs
- Consider getting baseline serum K⁺

**CASE**

- 87 y/o female with nausea & abdominal pain for 3 d
  - 3 d PTA started on TMP/SMX for urinary symptoms and pos UA
- Na 119 (baseline 130), K 4.2, Cl 90, Cr 0.6
- Hyponatremia
- Constipation

**TRIMETHOPRIM & HYPONATREMIA**

- Structurally related to amiloride
  - Blocks reabsorption of Na at the epithelial sodium channel (ENaC) in the distal nephron and leads to hyponatremia, hyperkalemia, and metabolic acidosis
- Under recognized adverse effect
- Greater risk with high-dose

**CASE – July 30**

- 68 y/o female with SOB, dry cough, fever
  - Present for 2 wks and worsening
  - Not been eating, weight loss, weak, shaky, chills, night sweats, DOE
- HTN, RA, osteoporosis
- Meds:
  - Infliximab (Remicade) started 6/19 with repeat 7/11; Prednisone 2.5 mg/d; hydroxychloroquine 200 mg 2xd; MTX 20 mg/wk; Leflunomide 10 mg/d;
  - ASA 81 mg/d; Losartan 50 mg 2xd; CTD 25 mg/d

**Readmission Aug 14**

- Unresponsive, vomited, bowel/bladder incontinence, tongue bleeding
  - EMS obtained PG 20
- Current meds:
  - TMP/SMX 2 DS 3xd since Aug 1
  - Prednisone 40 mg/d since Aug 2
  - Sertraline 25 mg/d
  - ASA 81 mg/d
  - Losartan 50 mg 2xd

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Pneumocystis

- Fungus
- Pneumocystis pneumonia (PCP) caused by Pneumocystis jirovecii PJP
  - Pneumocystis carinii now refers only to the Pneumocystis that infects rats
  - PJP refers to species that infects humans
- Immunosuppressive meds
  - CD4 count <200 is a major risk factor

Ann Pharmacother 16;50:673-9

INDICATIONS FOR PRIMARY PROPHYLAXIS/CHRONIC SUPPRESSION

- HIV/AIDS CD4 count < 200 cells/μL
- Equivalent of ≥ 20 mg Prednisone/d ≥ 1 mon
- Alemtuzumab (CLL), Temozolomide
  Hematopoietic & solid organ transplant during immunosuppression
- Fludarabine (hematologic malignancy)
- Wegener's granulomatosis on prednisone/ cyclophosphamide

Sanford Guide Web edition. Modified 6/20/18
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Downloaded 12/19/18

TMP/SMX HYPOGLYCEMIA

- SMX contains sulphanilamide group
  - Similar to sulfonylureas
  - May act on pancreatic islet cells increasing insulin secretion
- Dose challenge cases
  - Increased serum insulin & C-peptide levels

Sanford Guide Web edition. Modified 6/20/18
J Clin Oncol 36:3043-3054
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Downloaded 12/19/18
RISK FACTORS

- High dose (e.g., for PCP)
  - Has been reported with usual dosages (e.g., UTI, SSTIs)
- Prolonged administration
- Renal or liver dysfunction
  - SMX renally eliminated – higher serum levels
- Concurrent with DM agents
  - Sulfonylureas increase risk 6.6 times
  - Also reported in those not taking DM agents
- Malnutrition

TMP/SMX HYPOGLYCEMIA

- Rare but can be severe
  - Reports in HIV and non-HIV patients (e.g., UTI)
  - In PCP often with prednisone which should usually increase PG or at least prevent significant reduction in PG
- Onset about 3-10 d after starting TMP/SMX
- May be underestimated and underreported
- Potentially serious complication should be taken into consideration when prescribing

CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

-“NOT RISKY?” mnemonic
- Neurologic Effects
  - Aseptic meningitis with high dosages – uncommon
  - Risk with autoimmune diseases and HIV
  - Tremor – rare
  - Delirium – relatively uncommon
    - Risk in elderly, neurologic injury, metabolic disturbances
  - Gait disturbances – rare

- Toxic epidermal necrolysis (TEN) & allergy
  - Immune-mediated idiosyncratic reaction
  - Fever, rash, blood dyscrasias, SJS, TEN, DRESS, cholestatic or hepatocellular hepatitis, AIN – uncommon
  - Exanthesms & fixed drug eruptions – common

CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- Oxygen-carrying capacity & Other heme
  - Methemoglobinemia in < 6 wks age – rare
  - Blood dyscrasias – uncommon
    - Risk in malnutrition, G6PD deficiency
- Toxic epidermal necrolysis (TEN) & allergy
  - Immune-mediated idiosyncratic reaction
  - Fever, rash, blood dyscrasias, SJS, TEN, DRESS, cholestatic or hepatocellular hepatitis, AIN – uncommon
  - Exanthesms & fixed drug eruptions – common

HEME ADVERSE EFFECTS

- Bone marrow suppression
  - Folic acid inhibition – risk with poor nutrition, MTX
    - Megaloblastosis, thrombocytopenia
  - Hypersensitivity
    - Any heme effect with fever, rash
- Hemolytic anemia – risk with G6PD deficiency
- Thrombocytopenia
  - Ab-mediated destruction of platelets
HEME ADVERSE EFFECTS

- Methemoglobinemia – risk in < 6 wks old
  - Increase in methemoglobin (iron moiety in Fe3+ state instead of usual Fe2+ state
  - Cyanosis, "chocolate-colored" blood, and falsely low O2 sat with normal pO2
- Periodic monitoring of CBC with high-dose, extended use

CASE

- 82 y/o with rash and weakness
  - 2-d h/o diarrhea and weakness
  - Chill, sweats with no documented fever
  - Total body rash over last 2 d and bleeding from blisters on tongue and cheek
  - Recent reduction in Prednisone dose for PMR
    - Was taking 20 mg/d and 2 d ago down to 15 mg/d
  - L armpit cellulitis treated with TMP/SMX for 2 wks. Finished 3 d ago
- CABG, TIA, PMR, Addison's, B12 deficiency

Assessment

- Thrombocytopenia and anemia
- Differential
  - Microangiopathic hemolysis
  - Thrombotic thrombocytopenic purpura
  - Drug-induced immune-mediated
  - HUS-like syndrome with the diarrhea
  - Infectious diarrhea since immunocompromised
- With steroids, platelet & blood transfusion
  - 3 days later plt 119,000
  - Hgb 7.6 and stable

Drug-induced Thrombotic Microangiopathy (DITMA)

- Immune-mediated
  - Ab that react with multiple cells, including platelets, neutrophils, and endothelial cells
  - Binding only occurs in the presence of the drug
  - Described as drug-dependent Ab
- Drug-induced immune thrombocytopenia (DITP)
  - Platelets only target of drug-dependent antibodies

DITMA

- Microangiopathic hemolysis
  - Schistocytes on peripheral blood smear, anemia
- Negative Coombs test
- Increased LDH
- Thrombocytopenia may be mild to severe

Up-to-Date

1 month later

- L leg cellulitis treated as outpatient with linezolid 600 mg 2xd for 10 d with routine CBC
  - Platelet 48,000
  - I & D of draining abscess – MRSA
- Received vanco, then ceftaroline while in hospital – Doxycycline po on discharge
CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- Reproductive toxicity
  - Structural malformations (neural tube, CV and possible oral cleft and urinary system – uncommon
    - Risk with low folic acid & exposure during 1st trimester
  - Small-for-gestational age – uncommon
    - Risk with exposure 2nd & 3rd trimesters
  - Hyperbilirubinemia – rare
    - Risk with exposure after 32 wks

- Interactions – DDIs – common
  - Inhibits CYPP450 isoenzymes 2C8 (TMP) & 2C9 (SMX)
    - Warfarin, sulfonylureas, meglinitides, NSAIDs, fluvastatin, phenytoin
  - Organic anion transporter inhibitor in renal tubule
    - Reduce elimination of MTX (also anti-folate), Li++
    - Hyperkalemia with ACEIs/ARBs, NSAIDs, K-sparing diuretics

- Sugar
  - Hypoglycemia
    - Common with DDI
    - Rare when used alone
    - Risks renal dysfunction, high-dose, sulfonylureas
    - Reduce dose with CrCl < 30 mL/min

- Hyperkalemia & other kidney effects
  - Hyperkalemia – common & predictable
    - Risks renal dysfunction, high-dose, elderly, DM, ACEIs/ARBs, K-sparing diuretics, NSAIDs
  - AIN – uncommon
  - Obstructive tubulopathy – uncommon
  - Hyponatremia – uncommon

- Why? – Why not consider an alternate abx

CMAJ 11;183:1851-8

SUGGESTIONS FOR REDUCING RISKS IN USE OF TMP/SMX

- Rx alternate abx if clinically indicated
  - Esp. Pgy 1st trimester, G6PD deficiency, MTX
- Monitor electrolytes within a few days
  - Renal dysfunction, DM, elderly and AIDS
  - High-dosages
  - ACEIs, ARBs, K-sparing diuretics, NSAIDs
- INR within 3-4 d
- Monitor PG within a few d
  - Oral hypoglycemics, High-dosages, extended time

CMAJ 11;183:1851-8

CASE

- 65 y/o female presents with 3 d of watery diarrhea with flecks of blood
  - At least 11 episodes so far today with diffuse abdominal pain and cramping
  - Also c/o mild nausea, weakness and chills
- 10 d prior received Clindamycin from dentist for a dental infection
- 115/72; HR 105; 38.2
- WBC 15,750; Cr 1.5 (1.1)
- C. diff – positive
Clostridioides difficile Infection (CDI)
- New name for Clostridium difficile infection
- ~500,000/y in US
  - Most common nosocomial pathogen
  - ~25% community-acquired
- Infections
  - Fulminant colitis in 3-8% – Mortality 30-90%
  - Pseudomembranous colitis (PMC)
  - Toxic megacolon, Colon perforation, Sepsis
  - Death
- Linked to ~30,000 deaths/y vs 32,000 in traffic accidents

C. DIFFICILE PATHOGENESIS
- Anaerobic, gram-positive spore-forming bacillus
  - Releases a toxin which causes infection
  - Spores resistant to heat, acid, antibiotics
- Normal GI flora form protective barrier to prevent C. difficile colonization
- Antibiotics disrupt normal flora
  - Most important modifiable risk factor
  - Colonization with toxigenic strain of C. difficile
  - Toxins A and B are released

RISK OF C. diff DIARRHEA

<table>
<thead>
<tr>
<th></th>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents</td>
<td>Clindamycin</td>
<td>Cephalosporins</td>
<td>FQ</td>
</tr>
<tr>
<td></td>
<td>Other penicillins</td>
<td>Macrolides</td>
<td>TMP/SMX, Sulfonamides</td>
</tr>
<tr>
<td>Toxins</td>
<td>Aminoglycosides, Bacitracin</td>
<td>Carbenapemens, Daptomycin</td>
<td>Metronidazole, Nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td>Rifampin, Rifaximin</td>
<td>Tetracyclines, Tigecycline</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

Infection Severity
- Initial episode
  - Non-severe: WBC < 15,000 AND Scr < 1.5
  - Severe: WBC > 15,000 OR Scr > 1.5

Clinical Status
- Hypotension or shock, ileus, megacolon

Therapy
- Vancomycin 125 mg po 4xd X10d OR Fidaxomicin 200 mg 2xd X10 d
- Vancomycin 500 mg PO/NG qid (if ileus) PLUS Metronidazole 500 mg IV q8h (if ileus)

Choice of Agents

<table>
<thead>
<tr>
<th>Infection Severity</th>
<th>Clinical Status</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode</td>
<td>Vancomycin 125 mg po 4xd X10d OR Fidaxomicin 200 mg 2xd X10 d</td>
<td></td>
</tr>
<tr>
<td>Non-severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dental Infection
- Immunocompetent
  - Oral anaerobes (75%) Peptostreptococcus, Fusobacteria, Prevotella spp, Actinomyces, etc.
  - Facultative anaerobes include
    - Aerobes (25%) S. pyogenes, S. viridans group and S. anginosus group, other Strep
    - ≥ 19% resistant to PCN but may not cause abx failure

Sanford Guide Web edition. Modified 7/5/18
Journal of Oral and Maxillofacial Surgery, 2017-12-01, Volume 75, Issue 12, Pages 2606.e1-2606.e11
TREATMENT

• Non-severe infection
  – Amoxicillin/clavulanate 875/125 mg 2xd or 2000/125 mg 2xd
  – If allergic to penicillin Clindamycin 300 mg 4xd

Sanford Guide Web edition. Modified 7/5/18

• Penicillin
  – Facultative Strep predominate in early infection
  – < effective beyond 3-4 d of onset (gram neg anaerobes increase in number)
  – Historically was drug of choice


TREATMENT

• Amoxicillin no better spectrum than PCN
• Clindamycin
  – Excellent coverage of organisms
  – Penicillin allergy can use
• Metronidazole plus penicillin
  – Covers anaerobes and aerobes
• Azithromycin
  – Covers mouth anaerobes and aerobes
  – Penicillin allergy can use


CLINDAMYCIN

• Diarrhea ~20%
• C. diff colitis 10%
• J Hand Surg 14;39:989-91
• Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, Updated Edition, 29.e6

ENTITIES UNDER THE UMBRELLA OF UTIs

• Asymptomatic bacteriuria (ASB)
• Acute uncomplicated cystitis
• Recurrent cystitis
• Catheter associated ASB
• Catheter associated UTI (CAUTI)
• Prostatitis
• Pyelonephritis

In the Clinic: UTI. Ann Intern Med 10/3/17

UNCOMPLICATED UTI

• Can include cystitis or pyelonephritis
• Minimal comorbidities, normal urinary tract, not pregnant, premenopausal
  – Nonpregnant females 15-45 y who are otherwise normal and healthy
• Low risk for non E.coli, resistant pathogen or treatment failure
• Predictable response to antibiotics

COMPLICATED UTI

- Men, DM, pregnant, postmenopausal, pyelo within 1 y, multidrug-resistant pathogen, symptoms > 7 d, hospital-acquired, renal failure, obstruction (e.g., BPH, stones), indwelling cath or tubes, recent instrumentation, recent antibiotics, anatomic abnormality, transplant, immunosuppressed, UTI in childhood
- Greater incidence of pathogens other than E. coli and increased antibiotic resistance
- Less predictable response to antibiotics

NON CLASSIC COMPLICATED DEFINITION

- Some do not use the classic definitions of uncomplicated and complicated UTI
- Uncomplicated cystitis
  - Infection of the bladder in a nonpregnant adult
  - No systemic s/s beyond the bladder
- Complicated UTI
  - Infection extends beyond the bladder
  - Pyelonephritis is a complicated UTI regardless of patient characteristics

BACTERIAL ETIOLOGY

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>% Uncomplicated</th>
<th>% Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>70-95</td>
<td>21-54</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>1-2</td>
<td>1-10</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>1-2</td>
<td>2-17</td>
</tr>
<tr>
<td>Citrobacter spp</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>&lt;1</td>
<td>2-10</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>&lt;1</td>
<td>2-19</td>
</tr>
<tr>
<td>Other gram-neg</td>
<td>&lt;1</td>
<td>6-20</td>
</tr>
<tr>
<td>Coagulase-neg Staph</td>
<td>8-15%</td>
<td>1-4</td>
</tr>
<tr>
<td>Enterococci</td>
<td>1-2</td>
<td>1-23</td>
</tr>
<tr>
<td>Group B Strep</td>
<td>&lt;1</td>
<td>1-4</td>
</tr>
<tr>
<td>S. aureus</td>
<td>&lt;1</td>
<td>1-2</td>
</tr>
<tr>
<td>% saprophyticus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALTRU ANTIBIOMGRAM – E. coli % RESISTANT
EMPIRIC THERAPY OF UNCOMPPLICATED CYSTITIS

- Preferred
  - TMP/SMX DS 2xd or TMP 100 mg 2xd for **3 d**
  - Don’t use if local resistance > 20% or used within 3 mon
  - Nitrofurantoin 100 mg 2xd for **5 d**
  - Fosfomycin 3 gm **single dose**

- Alternative
  - β-lactams for **5-7d** (eg, amox/clav, cephalexin)
  - Cipro 250 mg 2xd or Levo 250 mg/d for **3 d**
  - Risk may outweigh benefit
  - Increasing resistance


EMPIRIC THERAPY OF COMPLICATED CYSTITIS

- **GET a UC**
  - Potential resistant pathogens or non E. coli etiology
  - Ciprofloxacin 500 mg 2xd for **7 d**
  - Levofloxacin 750 mg 1xd for **7 d**
  - Adjust antibiotic based on UC results

NITROFURANTOIN

- Renal Function Dosing
  - Normal renal function
  - NFN monohydrate/macrocrystals 100 mg bid
  - May see warning to not use if GFR < 60 due to low urine concentrations
    - CrCl 30-60 use usual dose
    - CrCl <30 do not use especially if ≥65 y
    - Urinary levels may not be sufficient in reduced renal function


FOSFOMYCIN IN CYSTITIS

- Single 3 g dose for cystitis
  - Inferior compared to other short-course regimens
    - ~$95 vs. NFN ~$35 vs. TMP/SMX ~$7 (UpToDate)
    - 9% diarrhea vs 6% nitrofurantoin vs 2.3% TMX
  - Possible choice
    - Minimal resistance and low collateral damage (e.g., on intestinal flora)
  - **NOT in pyelonephritis** – poor renal tissue levels


5-DAY NFN VS FOSFOMYCIN UNCOMPPLICATED UTI

- RCT 513 in Switzerland, Poland, Israel
  - Cystitis symptoms, dipstick positive UA, no h/o resistant uropathogens to NFN or FOS
  - NFN macro 100 mg 3xd X 5d vs FOS 3 g single
    - Not blinded for drug
  - Clinical resolution 28d: 70% vs. 58% (p<0.004)
    - E. coli 78% vs. 50%
  - Micro resolution: 74% vs. 63% (p=0.04)
    - E. coli 72% vs. 58%

JAMA 18:319:1781-9

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SANFORD – FARGO
2016 E. coli Resistance – Urine

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Outpatient</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>
CASE
• 18 y/o female with dysuria & frequency
  – 2 d onset of dysuria, frequency, urgency and hematuria, L back pain
  – Decreased appetite, nausea
  – Cystitis 2 months ago – resolved with TMP/SMX
• 110/68, 90, 38C
  – L CVA tenderness
• Nitrite pos; protein 300; WBC 20-50
• CBC: WBC 14
• HCG neg

Acute pyelonephritis
• Patient want to try outpatient with oral TMP/SMX since that worked last time
• Your response to abx request?
• She received Ciprofloxacin
• UC – E. coli
  – Resistant: Ampicillin, Ampicillin/Sulbactam, TMP/SMX
  – Sensitive: Cefazolin, Ceftriaxone, Ciprofloxacin, Gentamicin, Nitrofurantoin, Tobramycin

CHOOSING EMPIRIC AGENT FOR AN INPATIENT
• Abx susceptibility of prior UTI strains
• Local antibiogram
• Exposure to same class in past 3-6 mon - choose alternative agent
• Severity of illness and co-morbidities
• Use carbapenem (meropenem, imipenem, doripenem or ertapenem) if ESBL strain is known or suspected
• Consider vancomycin if Gram stain shows Gram-positive cocci

NEJM 12;366:1028-37

“Over the last 20 years there has been erosion of fluoroquinolones in terms of their spectrum of coverage especially for gram-negative pathogens. Even fluoroquinolone coverage for common pathogens such as Escherichia coli and Proteus mirabilis has been reduced to the point that these agents cannot be reliably depended on by themselves to offer adequate initial empirical coverage.”

Crit Care Clin 11;27:95-106

EMPIRICAL TREATMENT OF ACUTE PYELONEPHRITIS

OUTPATIENT ANTIBIOTICS
• “The rising prevalence of E. coli resistant to FQs & TMP/SMX complicates empirical oral therapy. In patients who receive oral treatment from the outset, depending on the likelihood of resistance, an initial dose of a supplemental, long-acting, parenteral antimicrobial agent (e.g., an aminoglycoside, ceftriaxone, or ertapenem) may be appropriate, and close follow-up is warranted.”

NEJM 18;378:48-59

• Outpatient
  – Cipro for 5-7 d or Levofloxacin for 5-7 d
  • 1st-line empiric therapy (2nd-line for cystitis)
  • If local resistance is < 10%
    • If >10% resistance or patient risk factors increase likelihood of resistance initial dose of ceftriaxone, ertapenem or aminoglycoside is often warranted
  – TMP/SMX for 10-14 d if pathogen susceptible
    • Due to resistance initial dose (above) often warranted
  – Oral 3rd gen Ceph for 10-14d may be effective


Dis-a-Mon 15;61:45-59
In the Clinic: UTI. Ann Intern Med 10/3/17

NEJM 18;378:48-59
EMPIRICAL TREATMENT OF ACUTE PYELONEPHRITIS

• **Inpatient - IV agents**
  - Choice based on local susceptibility & risk factors for resistance
  - FQ alone not recommended
  - Ceftriaxone or Cefepime monotherapy 7-10d
  - Piperacillin/tazobactam monotherapy 10-14d
  - Ertapenem or Meropenem monotherapy 7-10d
  - Aminoglycoside monotherapy 7-10d
  - Add vanco if MRSA or enterococcus (or ampicillin)

IDSA Guidelines. Clin Infect Dis 11:151.e103-e120
NEJM 12;366:1028-37
Disease-a-Month 13;61:43-59
NEJM 18;378:48-59

FDA FQ SAFETY COMMUNICATION – 7/26/16

• “disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system”
• “should be reserved for use … no other treatment options for acute bacterial sinusitis, ABECB, and uncomplicated UTIs … risk … generally outweighs the benefits”
• “some serious bacterial infections benefits … outweigh risks …available as … option.”

http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm

FQ ADVERSE EVENTS

• CNS up to 3%
  - Dizziness, headache, sedation and insomnia most common
  - Also confusion, seizure, agitation, depression, mood, psychosis, hallucinations
  - Risk with renal failure, electrolyte abnormalities, elderly, NSAIDs, high dose
  - > Cipro
• Peripheral neuropathy
  - Rapid onset and may be irreversible and severe

FQ FDA SAFETY COMMUNICATION 2018

• CNS effects differed for each FQ label
  - Nervousness, agitation, and disorientation had been listed in the labels
  - To add disturbances in attention, memory impairment, and delirium
  - Listing of psychiatric AEs will be more prominent and consistent across all FQs
  - Warn patients
  - Stop FQ for any CNS side effect


CASE

• 74 y/o female with L hip fx
• COPD, HTN, DM
• ASA, Duloxetine, Losartan, Prednisone 5 mg/d, Tiotropium, Budesonide nebs, Omeprazole, Insulin glargin 10 units (held)
• 2 d s/p gamma nail of hip s/s cystitis
  - Ciprofloxacin 500 mg 2xd
• Unresponsive – PG 17 at 2255
  - PG 294 at 2035 – insulin lispro 10 units SC

FQ FDA SAFETY COMMUNICATION 2018

• Hypoglycemia that may be severe – coma, death
  - Hypoglycemia coma with 67 reports
  - 13 deaths, 9 did not fully neurologically recover
  - > risk elderly and DM on meds, CKD
  - Monitor PG
  - Educate patient on s/s hypoglycemia and how to treat

FQ FDA SAFETY COMMUNICATION 2018

- Do not Rx if have other treatment options
  - Acute bacterial sinusitis, ABECB, and uncomplicated UTIs
  - Risks outweigh benefits
- "treatment of serious bacterial infections – such as certain types of bacterial pneumonia … benefits … outweigh the risks."
- Practitioners and patients consider risks and benefits to be informed about their use


FQ ADVERSE EVENTS

- AIN – infrequent
- Associated with aortic aneurysm & dissection
  – OR 2.25 – 2.79
  – Aneurysm NNH 618 > 65 y
  – 82 cases by 60 d per 1 million treatment episodes

CASE

- 49 y/o female
- GERD, chronic back pain, depression
- Meds:
  - Gabapentin 600 mg 3xd
  - Omeprazole 20 mg/d
  - Fluoxetine 40 mg/d
  - Trazodone 100 mg/d at bedtime

GABAPENTINOIDS

- Gabapentin (Neurontin, gen) $50-100/mon
- Pregabalin (Lyrica) $500-800/mon
- Immediate & extended release (> $) available
- Effective against partial-onset seizures
  - Major use neuropathies (DM, post-herpetic)
  - Fibromyalgia, chronic back pain, anxiety, restless leg syndrome, perioperative pain
- **Titrate dose to reduce adverse effects**
  - Wks for gabapentin, faster pregabalin

GABAPENTINOIDS

- Dose-related adverse effects
  - Ataxia, dizziness, fatigue, sedation, nystagmus, blurred vision, confusion, dependence (> pregabalin due to potency, fast absorption, > with opioid and benzodiazepine abuse)
- Non-dose-related adverse effects
  - **Edema**, weight gain
  - Behavioral changes in children
  - Rare stevens-johnson syndrome