THERAPEUTIC CASE STUDIES

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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.

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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

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- 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

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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

Am J Physiol Renal Physiol 03;284:F11-21

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LOOP DIURETICS

- 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

Am J Physiol Renal Physiol 03;284:F11-21

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LOOP DIURETICS

	Furosemide	Bumetanide	Torsemide
Usual dose	20-160 mg/d	0.5-4 mg/d	10-80 mg/d
Ceiling dose nl renal CrCl 20-50 CrCl < 20	 80-160 mg 160 mg 400 mg	 1-2 mg 2 mg 8-10 mg	 20-40 mg 40 mg 100 mg
Bioavailability	10-100% (~50%)	80-90%	80-100%
Half-life	0.3-3.4 h	0.3-1.5 h	3-4 h

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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

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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**

Sem Neph 11;31:483-94 J Cardiovasc Pharm Ther 14;19:5-13 NEJM 17;377:1964-75
Curr Heart Fail Rep 17;14:127-33 Heart Failure Clin 17;13:503-12
Ther Adv Cardiovasc Dis 17;11:271-8

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	Renal insufficiency		**Heart failure**
	Moderate	Severe	
Mechanism of ↓ response	Impaired diuretic delivery to site of action – reduced excretion		↓ Nephron response
Therapeutic strategy	Administer high enough dose to attain effective diuretic excretion rates at site of action		Increase the frequency of **effective** dose
Ceiling dose (mg, IV)			
Furosemide	80-160	160-200	40-80
Bumetanide	4-8	8-10	1-2
Torsemide	20-50	50-100	10-29

Am J Physiol Renal Physiol 03;284:F11-21

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LOOP DIURETICS IN ACUTE HF

- Goal is UO of 3-5 L/d until euvolemic
- 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 = bumetnide 1 mg = torsemide 20 mg

NEJM 17;377:1964-75

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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

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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).

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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

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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)

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	$/month	Medicare Out-of-Pocket $
Warfarin	< 10 (add INR monitoring)	
Dabigatran (Pradaxa)	~400 Savings card	
Rivaroxaban (Xarelto)	~419 Savings card	74-146
Apixaban (Eliquis)	~419 Savings card	74-147
Edoxaban (Savaysa)	~336 Savings card	

Med Lett Drug Therapeutics 18;60:41-8. Wholesale acquisition cost.
NEJM 18;279:2292

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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

North American Thrombosis Forum, AF Action Initiative Consensus Document. AJM 16;129:S1-S29 Thromb Haemost 2018;118:437-50

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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

AJM 16;129:S1-S29 Med Clin N Am 15;99:759-80
AHA NOACs Statement. Circ 17;135:e604-33 Thromb Haemost 18;118:437-50

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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. apixiban) 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
AHA NOACs Statement. Circ 17;135:e604-33 Thromb Haemost 18;118:437-50

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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

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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

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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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	5/28/16	**2/20/17**	**10/30/17**	**11/12/17**	11/20/17	11/21/17
CK					37	
BUN	16	15	16	14	45	30
Cr	1.2	1.2	1.3	1	2.2	1.3
Alb	4.1	4.1	3.7	3.9	4.1	
Alk Phos	70	**71**	**331**	**165**	**122**	
TBili	0.9	**0.8**	**1.7**	**0.9**	**1.1**	
AST	19	**19**	**71**	**19**	**21**	
ALT	15	**14**	**89**	**16**	**26**	

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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

Drug-induced Hepatotoxicity. 2009 http://emedicine.medscape.com/article/169814-overview

- > 1000 hepatotoxic meds/supplements

Curr Opin Gastroenterol 12;28:198-202 Clin Liver Dis 13;17:565-73

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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**

Drug Safety 09;32:55-68 Clin Liver Dis 13;17:507-18 Clin Liver Dis 13;17:565-73
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
ACG DILI Guideline Am J Gastroenterol 14;109:950-66

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Commonly used meds causing DILI

- Necrosis
  - **Acetaminophen**, ketoconazole, 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

Crit Care Med 10;38[Suppl.]:S175–S187

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LIVERTOX

DRUG-INDUCED LIVER INJURY

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Library of Medicine. http://livertox.nih.gov

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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

J Antimicrob Chemother 11;66:1431-46
Gastroenterol Clin N Am 46 (2017) 273-296
Clin Liver Dis 21 (2017) 35-54
https://livertox.nlm.nih.gov//AmoxicillinClavulanate.htm

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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)

Product information 9/09. http://us.gsk.com/products/assets/us_augmentin.pdf
J Antimicrob Chemother 11;66:1431-46 Gastroenterol Clin N Am 46 (2017) 273-296
Clin Liver Dis 21 (2017) 35-54 https://livertox.nlm.nih.gov

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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

J Antimicrob Chemother 11;66:1431-46 Gastroenterol Clin N Am 46 (2017) 273-296
Clin Liver Dis 21 (2017) 35-54 https://livertox.nlm.nih.gov//AmoxicillinClavulanate.htm

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MEDICATION ERRORS

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

The Joint Commission. National Patient Safety Goals. March 5, 2010. http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/npsg8_review.htm

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- 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)

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- 79 y/o male with n & v, dizziness and diaphoresis with near syncope
  - 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

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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."

Institute for Healthcare Improvement. Medication Reconciliation Review. Accessed 3/15/15 http://www.ihi.org/knowledge/Pages/Tools/MedicationReconciliationReview.aspx

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

Gooen LG. Clin Geriatr Med. Online 3/1/17 http://dx.doi.org/10.1016/j.cger.2017.01.006

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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**

Institute for Healthcare Improvement. Medication Reconciliation Review. Accessed 3/15/15 http://www.ihi.org/knowledge/Pages/Tools/MedicationReconciliationReview.aspx

Prevent Adverse Drug Events by Implementing Medication Reconciliation. Cambridge, MA: Institute for Healthcare Improvement; 2011. (www.ihi.org)

Mayo Clin Proc 14;89:1116-25

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HYPOGLYCEMIA CASE

- 59 y/o female found unresponsive
  - EMS reported PG 12
  - Per home health last insulin dose last night
  - Has had several ED visits & hospitalizations for hypoglycemia
    - Home dose administered in hospital no hypoglycemia
- DM, LDL, mild intellectual disability, MDD
  - Neuropsych testing – competent to make decisions
  - Administers her own meds
  - Home health daily

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- 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

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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

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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.

Pharmacist's Letter/Prescriber's Letter. December 2016

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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.

Pharmacist's Letter/Prescriber's Letter. December 2016

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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

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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

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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

Hankey GJ. Edit. NEJM 13;369:82-3

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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

NEJM 11;365:993-1003

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SEVERE INTRACRANIAL MAJOR ARTERY ATHEROSCLEROSIS

- "typically treated with DAPT for 3 mon or longer (consistent with results of … SAMMPRIS trial"

Grotta JC. Edit. NEJM 18;379:291-2

- 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

Med Clin N Am online 11/28/18 https://doi.org/10.1016/j.mcna.2018.10.001
Neurobiology of Disease 19;124:118-32

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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)

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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

Stroke 18;49:e46-e99

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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)**

NEJM 18;379:215-25

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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

Grotta JC. Edit. NEJM 18;379:291-2

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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

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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

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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

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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

Pharmacist's Letter/Prescriber's Letter. January 2015

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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 14;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

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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^+**

PL Detail-Document, Trimethoprim, Hyperkalemia, and Meds that Increase Potassium. Pharmacist's Letter/Prescriber's Letter. January 2015.

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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

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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

Amer J Med 16;129:1322-8

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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

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- CXR: L basilar opacities (LLL pneumonia); bibasilar interstitial thickening
- CT chest: patchy bilateral ground-glass opacities with interlobular thickening, bilateral pleural effusions
- Presumed PCP pneumonia – empirical therapy
  - TMP/SMX DS 2 tabs q8h for 21 d
  - Prednisone 40 mg 2xd
- Improved on TMP/SMX
  - Sertraline 25 mg started
  - Discharged Aug 9 to TCU on TMP/SMX

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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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- All may be due to TMP/SMX
  - Acute AMS & seizure due to hypoglycemia
  - Na 122; K 5.4; ALT 58 (30 2 wks ago)
- D/C TMP/SMX
- Switch to clindamycin & primaquine for last 9 d of PCP therapy

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	8/1	**8/3**	**8/6**	**8/7**	**8/8**	**8/14**
Pred	5 mg	**80**	**80**	**40**	**40**	40
TMP/ SMX 2 DS 3xd	x	x	x	x	x	x
Na	138	134	**130**	**130**	**127**	**122**
K	4.1	4.7	5.6	5.1	4.6	**5.4**
PG	96	109	**93**	**78**	**67**	**20** by EMS; D10W 162

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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

PCP. Reviewed 7/25/17. https://aidsinfo-nih-gov.ezproxylr.med.und.edu/contentfiles/lvguidelines/adult_oi.pdf
Ann Pharmacother 16;50:673-9

63

PRIMARY REGIMENS

- **Adult treatment**
  - **TMP-SMX DS, 2 tabs po q8h** x 21 days PLUS
  - Prednisone 15-30 min before starting therapy:
    - 40 mg po q12h x 5 d
    - Then 40 mg q24h x 5 d
    - Then 20 mg q24h x 11 d
- Adult Prophylaxis
  - TMP-SMX-DS 1 tab po q24h or 3x/week OR TMP-SMX-SS 1 tab po q24h

Sanford Guide Web edition. Modified 6/20/18

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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 J Clin Oncol 36:3043-3054
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Downloaded 12/19/18

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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

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RISK FACTORS

- High dose (eg, for PCP)
  - Has been reported with usual dosages (eg, 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

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TMP/SMX HYPOGLYCEMIA

- Rare but can be severe
  - Reports in HIV and non-HIV patients (eg, 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

International Journal of Clinical Pharmacology and Therapeutics, Vol. 56 – No. 2/2018 (86-89)
BMC Endocrine Disorders (2016) 16:62 Europ Review Medical Pharmacolog Sci 10;14:1015-8
Nutrition 14;30:957-59 Renal Replacement Therapy 17;3:45 CMAJ 11;183:1851-8

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TMP/SMX USES

- Outpatient in skin & skin structure infections due to CA-MRSA
- UTIs
- Prostatitis
- Bronchitis, pneumoniae
- Drug of choice Pnuemocystis carinii (PCP) pneumonia (HIV patients)
- Acute otitis media, sinusitis
- Infectious diarrhea

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CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- "NOT RISKY?" mneomic
- **N**eurologic 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

CMAJ 11;183:1851-8

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CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- **O**xygen-carrying capacity & **O**ther heme
  - Methemoglobinemia in < 6 wks age – rare
  - Blood dyscracias – uncommon
    - Risk in malnutrition, G6PD deficiency
- **T**oxic epidermal necrolysis (TEN) & allergy
  - Immune- mediated idiosyncratic reaction
  - Fever, rash, blood dyscrasias, SJS, TEN, DRESS, cholestatic or hepatocellular hepatitis, AIN – uncommon
  - Exanthems & fixed drug eruptions – common

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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

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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

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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

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- 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 his CBC improved
  - 3 days later plt 119,000
  - Hgb 7.6 and stable

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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

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DITMA

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

Up-to-Date

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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

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CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- **R**eproductive 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

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CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- **I**nteractions – 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

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CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

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

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CONSIDERATIONS WHEN PRESCRIBING TMP/SMX

- Hyper**k**alemia & other **k**idney effects
  - Hyperkalemia – common & predictable
    - Risks renal dysfunction, high-dose, elderly, DM, ACEIs/ARBs, K-sparing diuretics, NSAIDs
  - AIN – uncommon
  - Obstructive tubulopathy – uncommon
  - Hyponatremia – uncommon
- **Y?** – Why not consider an alternate abx

CMAJ 11;183:1851-8

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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

83

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

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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

http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_HCP.html. Curr Opin Crit Care 07;13:450-5
NEJM 15;372:1539-48.

85

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
  - **Diarrhea and colitis occur**

J Clin Gastroenterol 07;41:S24–9. Lancet 08;371:1487-8. Clin Infect Dis 08;46(suppl 1):S19-31
Journal of Intensive Care Medicine 14;29:190-9 NEJM 15;372:1539-48

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RISK OF C. diff DIARRHEA

High Risk	Moderate Risk	Low Risk
Clindamycin	Other penicillins	Aminoglycosides Bacitracin
Cephalosporins	Macrolides	Carbapenems Daptomycin
FQ	TMP/SMX, Sulfonamides	Metronidazole Nitrofurantoin
Broad-spectrum PCN (e.g., amoxicillin)		Rifampin Rifaximin Tetracyclines Tigecycline Vancomycin

J Clin Gastroenterol 07;41:S24–9 J Intensive Care Medicine 14;29:190-9 NEJM 15;372:1539-48

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CHOICE OF AGENTS

Infection Severity	Clinical Status	Therapy
Initial episode Non-severe	WBC ≤ 15,000 **AND** Scr < 1.5	Vancomycin 125 mg po 4xd X10d OR Fidaxomicin 200 mg 2xd X10 d
Initial episode Severe	WBC ≥ 15,000 **OR** Scr ≥ 1.5	Vancomycin 125 mg po 4xd X10d OR Fidaxomicin 200 mg 2xd X10 d
Initial episode Fulminant	Hypotension or shock, ileus, megacolon	**Vancomycin 500 mg PO/NG** qid (If ileus, consider adding rectal vanco) **PLUS Metronidazole 500 mg IV** q8h (if ileus)

Clinical Practice Guidelines for C. difficile Infection in Adults and Children: 2017 Update by the IDSA & SHEA. Clin Infect Dis 18;66:987-94

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COMPARISON OF AGENTS

	Vancomycin	Metronidazole	Fidaxomicin
FDA-approved	Yes	No	Yes
Mild Disease Severe	++++ Superior	++ Inferior	++++ Superior
Relapse rate	10-25%	10-25%	≤ Vanco
Cost for 10 d	Capsules 125 mg: ~$500-600 Oral Soln (Firvanq): $125 IV taken po: ~$60 for 10d bitter taste	Tablets 500mg: ~$15 for 10 d	Tablets (Dificid) 200 mg: $3,700 for 10d

Adapted from Bartlett JG. Presented at 45th Annual Meeting of IDSA, 10/07. San Diego, CA
Cost from Pharmacist's Letter/Prescriber's Letter. April 2018.

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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

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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

Dental Clin North Amer 17;61:235-52

91

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

Dental Clin North Amer 17;61:235-52

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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

93

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

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- 68 y/o male with urinary tract symptoms
- Cystitis s/s, afebrile, no CVA
- UA positive
- UTI or prostatitis
- Complicated or uncomplicated
- FQ vs. Nitrofurantoin
  - NFN started
- UC P. rettgeri
  - R: NFN
  - S: FQ

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UNCOMPLICATED UTI

- Can include cystitis or pyelonephritis
- Minimal comorbidities, normal urinary tract, not pregnant, premenopausal

  AFP 11;84:771-6
  - **<u>Nonpregnant females 15-45 y who are otherwise normal and healthy</u>**
- Low risk for non E.coli, resistant pathogen or treatment failure
- Predictable response to antibiotics

NEJM 12;366:1028-37 Med Clin N Am 13;97:737-57 Prim Care Clin Office Pract 13;40:687-706

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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

NEJM 12;366:1028-37 Prim Care Clin Office Pract 13;40:687-706 PA Clin 18:3;55-67

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NON CLASSIC COMPLICATED DEFINITOIN

- 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

UpToDate Accessed 2/4/18

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- "Among women aged <u>18 to 70</u> years, acute uncomplicated UTI results in nearly 4 days of genitourinary symptoms and 3 days of restricted activity per episode."

Nitrofurantoin vs Fosfomycin. Rendering a Verdict in a Trial of Acute Uncomplicated Cystitis. edit. JAMA 18;319:1771-2

- "Acute uncomplicated UTI or cystitis refers to symptomatic bladder infection in women without structural abnormalities, urinary instrumentation, or systemic diseases such as immunodeficiency"

Can J Urol 12;19(suppl 1):42-8

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BACTERIAL ETIOLOGY

	% Uncomplicated	% Complicated
E. coli	70-95	21-54
P. mirabolis	1-2	1-10
Klebsiella spp	1-2	2-17
Citrobactor spp	<1	5
Enterobacter spp	<1	2-10
P. aeruginosa	<1	2-19
Other gram-neg	<1	6-20
Coagulase-neg Staph	5-15*	1-4
Enterococci	1-2	1-23
Group B Strep	<1	1-4
S. aureus	<1	1-2

*S. saprophyticus

Infect Dis Clin N Am 03;17:303-32. Prim Care Clin Office Pract 13;40:687-706

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Altru Health System

7/1/16 – 6/30/17

Organisms	Ampicillin	Tetracycline	Ceftriaxone	Cefotaxime	Penicillin IV (Non Meningitis)	Clindamycin	Erithromycin	Oxacillin	SXT	Vancomycin	Ertapenem	Ciprofloxacin	Gentamicin	Piperacillin/Tazobactam	Aztreonam	Meropenem	Cefepime	Ampicillin/Sulbactam
E. faecalis group	100	-	-	-	-	-	-	-	-	100	-	-	-	-	-	-	-	100
E. faecium group	23	-	-	-	-	-	-	-	-	41	-	-	-	-	-	-	-	-
S. aureus group	-	96	59	-	-	79	50	65	97	100	-	-	-	-	-	-	-	92
Staphylococcus aureus, Methicillin Resistant (MRSA)	-	95	-	-	-	69	-	-	98	100	-	-	-	-	-	-	-	-
Staphylococcus epidermidis	-	86	86	-	-	60	36	42	52	99	-	-	-	-	-	-	-	86
Streptococcus pneumoniae	-	98	-	100	100	100	56	-	85	100	-	-	-	-	-	100	-	-
E. coli group	62	90	97	-	-	-	-	-	85	-	100	97	96	97	98	91	98	99
E. aerogenes group	-	-	97	-	-	-	-	-	100	-	100	100	100	71	93	100	100	-
E. cloacae group	-	-	77	-	-	-	-	-	94	-	92	98	99	72	90	100	100	-
K. oxytoca group	-	-	95	-	-	-	-	-	97	-	100	99	100	95	97	-	100	61
K. pneumoniae group	-	-	99	-	-	-	-	-	96	-	50	98	99	99	96	-	-	90
P. aeruginosa group	-	-	-	-	-	-	-	-	-	-	-	60	86	80	80	95	83	-
P. mirabilis group	86	-	97	-	-	-	-	-	92	-	100	89	97	100	97	-	100	90
Serratia marcescens	-	-	98	-	-	-	-	-	100	-	100	91	100	53	100	-	100	-
Citrobacter group	-	100	82	-	-	-	-	-	93	-	93	98	98	75	85	67	94	-

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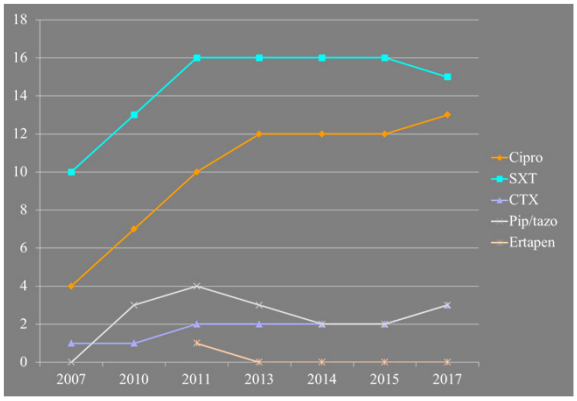
ALTRU ANTIBIOGRAM – E. coli % RESISTANT



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SANFORD – FARGO
2016 E. coli Resistance – Urine

	Outpatient	Inpatient
• Ciprofloxacin	15%	17%
• TMP/SMX	17%	22%
• Ceftriaxone	4%	6%
• Pip/Tazo	3%	4%
• Cefazolin	12%	14%
• Ertapenem	0%	0%
• Nitrofurantoin	3%	4%

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EMPIRIC THERAPY OF UNCOMPLICATED CYSITIS

- 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
  - ß-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

IDSA Guidelines. Clin Infect Dis 11;51:e103-e120

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EMPIRIC THERAPY OF COMPLICATED CYSITIS

- **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

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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

UTIs in Adults. Pharmacist's Letter/Prescriber's Letter. March 2018

106

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

IDSA Guidelines. Clin Infect Dis 11;51:e103-e120

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5-DAY NFN VS FOSFOMYCIN UNCOMPLICATED 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

108

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

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- 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

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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

111

"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

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EMPIRICAL TREATMENT OF ACUTE **PYELONEPHRITIS**

- **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

IDSA Guidelines. Clin Infect Dis 11;51:e103-e120. NEJM 12;366:1028-37. JAMA 14;311:844-54
Dis-a-Mon 15;61:45-59 In the Clinic: UTI. Ann Intern Med 10/3/17 NEJM 18;378:48-59

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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

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EMPIRICAL TREATMENT OF ACUTE PYELONEPHRITIS

- **Inpatient - IV agents**
  - Choice based on local susceptibility & risk factors for resistance
  - FQ alone **not** recommended NEJM 18;378:48-59 review
  - 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;51:e103-e120 NEJM 12;366:1028-37
Disease-a-Month 15;61:45-59 NEJM 18;378:48-59

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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

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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**

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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

https://www.fda.gov/Drugs/DrugSafety/ucm611032.htm. July 10, 2018

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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

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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

https://www.fda.gov/Drugs/DrugSafety/ucm611032.htm. July 10, 2018

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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

https://www.fda.gov/Drugs/DrugSafety/ucm611032.htm. July 10, 2018

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FQ ADVERSE EVENTS

- AIN – infrequent

Mayo Clin Proc 18;93:25-31

- Associated with aortic aneurysm & dissection
  - OR 2.25 – 2.79
  - Aneurysm NNH 618 > 65 y

AJM 17;130:1449-57

  - 82 cases by 60 d per 1 million treatment episodes

BMJ 2018;360:k678

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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

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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**

Pharmacist's Letter/Prescriber's Letter. August 2018.

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GABAPENTINOIDS

- Gabapentin 10th most commonly Rx'd med
- Pregabalin (Lyrica) 8th in cost
- Abuse is now common with high doses
  - Euphoria, relaxation, THC-like high, boosts high from opioids, sociability
- Taper dose ≥ 1 wk when discontinuing
  - Similar withdrawal as EtOH or benzodiazepines
- Pregabalin CS V – both reportable ND Rx drug monitoring program (PDMP)

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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

Pharmacist's Letter/Prescriber's Letter. August 2018.

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