GERIATRIC CLINICAL PEARLS

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CLINICAL PEARLS OBJECTIVES

- Identify risk factors associated with the development of catheter-associated UTIs (CAUTIs) and discuss the role of antibiotics in the treatment and prevention of CAUTIs.
- Evaluate the appropriate use of urinary anticholinergics related to correct indication, medication formulation, dosing, prevention of side effects, and goals for symptom improvement.
- Describe the risk factors and potential mechanism of SSRI-induced hyponatremia.
- Discuss issues associated with use of PPIs in older adults including infection risk and electrolyte malabsorption, and consequences in this population.
- Identify safety concerns of non-steroidal anti-inflammatory drugs (NSAIDs) in conjunction with other common medications prescribed in the geriatric population.

CATHETER-ASSOCIATED URINARY TRACT INFECTIONS (CAUTIS)

- Indwelling catheter
- Intermittent catheter
- External catheter
- Suprapubic catheter

INDICATIONS FOR CATHETERS

- Acute urinary retention or acute bladder outlet obstruction
- Patient requires strict prolonged immobilization or has diagnosis of neurogenic bladder
- Urologic surgery or other surgery on contiguous (adjacent) structures of the genitourinary tract

EPIDEMIOLOGY

Based on National Health and Safety Network Data (NHSN) in Long Term Care Settings:

- 40% of all healthcare-associated infections
- 13% of elderly have an indwelling catheter on admission to nursing homes
- Presence of bacteriuria is 1-10% in those aged 70 years and older
- “Urinary catheters inappropriately placed in 21-50% of patients”
**DEFINITION**

- Definition by the Infectious Disease Society of America (IDSA):
  - Symptoms plus $\geq 1 \times 10^3$ CFU/ml of $\geq 1$ bacterial species collected midstream
  - Blood in the urine
  - Pain/burning with urination
  - Frequent and strong urge to urinate
  - Pressure, pain, spasms in back or lower belly
  - Fever
  - Mental status changes or confusion (common in the elderly)

**RISK FACTORS FOR DEVELOPMENT OF CAUTI**

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of catheterization*</td>
<td>Female sex</td>
</tr>
<tr>
<td>Nonadherence to aseptic catheter care</td>
<td>Severe underlying illness</td>
</tr>
<tr>
<td></td>
<td>Nonsurgical disease</td>
</tr>
<tr>
<td></td>
<td>Age greater than 50</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine greater than 2 mg/dl</td>
</tr>
</tbody>
</table>

*May or may not be modifiable

**PATHOGENS IMPLICATED IN CAUTI**

- Most frequent pathogens: E. coli, Klebsiella, Staphylococcus, Proteus
- Concerns associated with antibiotic use
- Presence of biofilms
- Multi-drug resistance with recurrent antibiotic use

**CDC AND IDSA RECOMMENDATIONS FOR PREVENTION OF CAUTIS**

- Emphasizes appropriate indications for minimum duration possible and early catheter removal
- Importance of personnel hygiene and maintenance of catheter
- Hand hygiene and aseptic technique
- Metrics such as number of CAUTIs urinary catheter days/patient days
- Recommend against routine use of systemic antimicrobial prophylaxis

**IDSA TREATMENT RECOMMENDATIONS**

Obtain urine culture prior to initiating antimicrobial therapy
Replace catheters (source of infection)

**COMMON ANTIBIOTIC REGIMENS**

- Levofloxacin 250 mg daily x 7 days x or ciprofloxacin 500 mg BID x 5-7 days
- Sulfamethoxazole-trimethoprim DS x 7 days
- Cefuroxime 250 mg BID x 7-10 days
- Amoxicillin-clavulanate 875 mg BID x 10-14 days
PHARMACIST ROLE

As an outpatient/community pharmacist:
- When patient presents with recurrent Rsx for urinary antibiotics, ask if symptoms are improving with use of antibiotic.
- If your store sells foley catheters or medical supplies, ask about expected duration of catheter use.

As an inpatient provider:
- Review cultures and patient’s subjective report before verifying antibiotics.
- Recommend de-escalation when appropriate.

As a long-term care provider:
- If the patient is a nursing home resident, educate staff and other providers about prevention techniques.

PHARMACIST ROLE

OVERACTIVE BLADDER (OAB): CORRECT INDICATION

OAB Definition
- Overall syndrome of symptoms related to impaired urinary bladder detrusor muscle
- Estimated 43% of the population suffers from OAB
- American Urology Association (AUA) Guidelines: Non-pharmacologic therapies first-line
- Urinary Anticholinergics are classified as potentially inappropriate medications in older adults

Treatment dependent upon type of OAB

<table>
<thead>
<tr>
<th>Type of OAB</th>
<th>1st line</th>
<th>2nd line</th>
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<tbody>
<tr>
<td>Urge</td>
<td>Non-pharmacologic Therapy</td>
<td>Urinary anticholinergic</td>
<td>Symptom dependent</td>
</tr>
<tr>
<td>Stress</td>
<td>Non-pharmacologic Therapy</td>
<td>Non-pharmacologic Therapy</td>
<td>Symptom dependent</td>
</tr>
<tr>
<td>Mixed</td>
<td>Non-pharmacologic Therapy</td>
<td>Non-pharmacologic Therapy</td>
<td>Symptom dependent</td>
</tr>
</tbody>
</table>

URINARY ANTICHOLINERGICS: FORMULATION

Immediate-Release vs Extended-release
- Immediate Release formulation – 5mg TID
- Results in unreliable drug delivery
- Extended-Release formulation – 10mg OROS delivery system
- Achieves steady state of the drug over a 24 hour period

URINARY ANTICHOLINERGICS: THERAPEUTIC OPTIONS

Dry mouth
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Constipation</th>
<th>Dizziness</th>
<th>Somnolence</th>
<th>Blurred Vision</th>
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<tbody>
<tr>
<td>Anti-muscarinics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxybutynin IR</td>
<td>71%</td>
<td>15%</td>
<td>17%</td>
<td>14%</td>
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<tr>
<td>Oxybutynin ER</td>
<td>35%</td>
<td>9%</td>
<td>5%</td>
<td>6%</td>
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<tr>
<td>Oxybutynin Gel</td>
<td>7.5%</td>
<td>1%</td>
<td>3%</td>
<td>---</td>
</tr>
<tr>
<td>Oxybutynin Transdermal Patch</td>
<td>4%</td>
<td>3%</td>
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</table>

URINARY ANTICHOLINERGICS: THERAPEUTIC OPTIONS

<table>
<thead>
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<th>Generic Name</th>
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<th>Dizziness</th>
<th>Somnolence</th>
<th>Blurred Vision</th>
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</thead>
<tbody>
<tr>
<td>Anti-muscarinics</td>
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</tr>
<tr>
<td>Fesoterodine ER</td>
<td>19%</td>
<td>4%</td>
<td>&lt;1%</td>
<td>---</td>
<td>&lt;1%</td>
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<tr>
<td>Darifenacin ER</td>
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<td>15%</td>
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<td>---</td>
<td>&lt;2%</td>
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<tr>
<td>Solifenacin</td>
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<td>5%</td>
<td>2%</td>
<td>---</td>
<td>4%</td>
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<tr>
<td>Tizanidine LA</td>
<td>23%</td>
<td>6%</td>
<td>---</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Trospium XR</td>
<td>11%</td>
<td>9%</td>
<td>---</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

NON-ANTICHOLINERGIC THERAPEUTIC OPTION

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dry Mouth</th>
<th>Constipation</th>
<th>Hypertension</th>
<th>Headache</th>
<th>Anticholinergic Toxicity</th>
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<tr>
<td>Beta-3 Agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirabegron ER</td>
<td>---</td>
<td>2%</td>
<td>11%</td>
<td>2%</td>
<td>&lt;2%</td>
</tr>
</tbody>
</table>

SETTING GOALS

- Goals:
  - Improve symptoms
  - Improve ADLs
  - OAB can greatly impact activities of daily living (ADLs)
  - Anxiety
  - Depression
  - Psychosocial & social consequences

TITRATING DOSES & PREVENTION OF SIDE EFFECTS

First-Line Therapy
- Non-pharmacologic therapies
  - Bladder Training
  - Kegel Exercises

Second-Line Therapy
- Anticholinergic initiated at low dose
  - Titrated to symptom improvement
  - Urgency
  - Frequency
  - Nocturia
  - De-escalate/discontinue dose if patient starts to experience adverse effects
  - Dry mouth
  - Constipation
  - Impaired cognition
  - Glaucoma

PHARMACIST ROLE

- Pharmacists can improve quality of life in OAB patients by:
  - Evaluating if urinary anticholinergics are prescribed for the appropriate indication
  - Counseling/Ensuring adequate trial of non-pharmacologic therapies when appropriate
  - Recommending the ER formulation to minimize side effects
  - Titrating the dose for symptom improvement (lowest dose possible)
  - De-escalating/discontinue doses if a patient experiences adverse effects

SSRI-ASSOCIATED HYPONATREMIA
HYPONATREMIA BACKGROUND

- Serum sodium concentration < 135 mEq/L
- Normal serum sodium 135-145 mEq/L
- Associated with morbidity and mortality
- Cerebral edema
- Neurologic dysfunction
- Regulation of water and sodium balance
- Antidiuretic hormone (ADH)
- Excretion of excess water

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

- Depression in older adults (65 years and older)
- 15% Community-dwelling older adults
- 43% Older adults with extensive medical illness
-Selective serotonin reuptake inhibitors (SSRIs) most commonly prescribed
-Incidence of SSRI-associated hyponatremia up to 39% in older adults
-Risk higher with SSRIs vs other antidepressant medications

SSRI-ASSOCIATED HYPONATREMIA

- Mechanism not well established
- Syndrome of inappropriate antidiuretic hormone (SIADH)
- Unsuppressed ADH
- Prevents diuresis of excess fluid
- Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)
- Overexpression of water channel proteins
- Increased fluid retention

CLINICAL SIGNIFICANCE

Risk Factors
- Older age (65 years or more)
- Female gender
- Low body mass index (BMI)
- Low baseline serum sodium
- Comorbid conditions
- Heart failure, malignancy, adrenal insufficiency
- Risk elevated during initial treatment phase

Medications with Increased Risk
- Thiazide diuretics
- Loop diuretics
- Carbamazepine
- Theophylline
- Amiodarone

SHOULD THE SSRi BE DISCONTINUED?

Mild, asymptomatic hyponatremia
- Asymptomatic, presents with serum Na 130-134 mEq/L
- Address other reversible causes of hyponatremia
- Discontinuation may not be necessary if depressive symptoms improved
- Reduce dose or maintain current dose with fluid restriction

Moderate to severe hyponatremia
- Symptomatic
- Recent increased rate of falls
- Gait instability
- Refer patient to provider or ED
- Discontinuation of SSRi warranted
- Serum sodium correction

Cross-titration to antidepressants not associated with hyponatremia is a reasonable option (bupropion, mirtazapine, trazodone)

PHARMACIST’S ROLE

- Provide patient counseling regarding adverse effects of SSRIs and appropriate follow-up actions
- Recognize signs and symptoms of SSRI-associated hyponatremia
- Refer patients appropriately to providers
- Recommend antidepressants with low hyponatremia risk to providers
- Assist with cross-titration of antidepressant agents as necessary
PROTON PUMP INHIBITORS: RISK IN OLDER ADULTS

 increasing usage of proton pump inhibitors
- PPI use in ambulatory care settings more than doubled from 2002 to 2009
- 46.7% of patients taking PPIs were 65 years of age or older
- 62.9% of PPI users' indication for PPI unclear

Beers criteria consensus
- PPI added to Beers Criteria in 2015 due to Clostridium difficile infection (CDI) and fracture risk
- Complications of PPI use may be more common in older adults
- Specifically recommends avoiding PPI use exceeding 8 weeks without compelling indications
- Histamine-2 Receptor Antagonist (H2RA) when possible

Hypomagnesemia
- Older adults at higher risk for hypomagnesemia at baseline
- Symptoms include nausea, vomiting, diarrhea, cramps, tetany, confusion, or seizures
- Often associated with secondary hypokalemia or hypocalcemia
- Magnitude of risk: One study reports an odds ratio of 1.5 in adults >65 vs. ≤65 years old
- Possible mechanism: Impaired intestinal magnesium absorption due to less acidity facilitating absorption or impairment of active transport pathway.
- Pharmacist's role: Counseling of patients on long-term PPIs on other QT-prolonging agents

Clostridium difficile infection
- Adults ≥65 years old at highest risk; account for 92% of hospitalizations due to CDI
- Magnitude of risk: Based on available evidence, approximately 2-fold increased risk in older adults on PPIs
- Additional risk factors: recent antibiotic exposure, hospitalizations, increasing age
- Possible mechanism: Increased gastric pH allowing vegetative C. difficile to survive and/or due to changes in gut microbiome
- Pharmacist's role: Consider previous prescriptions that may indicate treatment for CDI

Fractures and falls
- 75% of hip, spine, and distal forearm fractures occur in older adults
- Significant morbidity and mortality
- Magnitude of risk: Up to 25-50% increased risk of hip fracture among older adults on PPIs
- Possible mechanism: Potential effects on trabecular (spongy) bone, or impaired absorption of calcium
- Absorption of calcium carbonate decreased from 9.1% to 3.5% in women 65-89 taking omeprazole
- Pharmacist's role: Counsel patients with increased risk including impairments in ambulation or taking other medications associated with falls
COMMUNITY-ACQUIRED PNEUMONIA (CAP)

- Older adults at higher risk for pneumonia than younger adults
- Hospitalization, death also more likely
- **Magnitude of risk**: Among studies that show a difference, approximately 30% higher risk of CAP
- Appears highest with recent initiation of PPI (<15-30 days)
- Unclear if risk persists with prolonged use
- **Possible mechanism**: Increased gastric pH → colonization of bacteria → aspiration
- **Pharmacist’s role**: Ensure counseling of patients already at risk.


VITAMIN B12 DEFICIENCY

- Vitamin B12 deficiency more common in older adults due to less gastric acid secretion
- Vitamin B12 bound to protein in meat and eggs; gastric acid required to release
- Deficiency can result in psychiatric, neurologic, or hematologic abnormalities
- **Magnitude of risk**: Up to 80% increased risk according to one meta-analysis
- **Possible mechanism**: Further reduction of gastric acid secretion in older adults may exacerbate already-impaired absorption of vitamin B12
- **Pharmacist’s role**: Be able to recognize symptoms of deficiency; consider those already at risk.


CHRONIC KIDNEY DISEASE (CKD)

- Older adults disproportionately affected by CKD and acute kidney injury (AKI)
- Lower renal function at baseline than younger adults
- Acute interstitial nephritis (AIN) may or may not be reversible
- **Magnitude of risk**: Potential 40-50% increased risk in older adults on PPIs
- Unclear if duration of PPI use is related
- **Possible mechanism**: PPI may cause AIN which may go undiagnosed, leading to chronic interstitial nephritis, ultimately resulting in CKD
- **Pharmacist’s role**: Counsel glycemic control in DM and discontinuing nephrotoxic agents such as NSAIDs.


DEMENTIA

- Dementia affects primarily older adults and may compromise independence
- **Magnitude of risk**: Potentially dose-dependent 40% increased risk
- **Possible mechanism**: PPI may cross blood-brain barrier → inhibit proton pumps on microglia cells → increased lysosome pH → decreased protease activity → less digestion of Aβ fragments (amyloid) → contributes to Alzheimer’s Disease
- **Pharmacist’s role**: Be mindful of concurrent prescriptions such as memantine, donepezil, rivastigmine, etc.


QUALITY OF EVIDENCE

- Appears likely that overuse of PPIs is associated with a variety of adverse effects particularly detrimental to older adults
- No randomized controlled trials; unlikely that any will be published
- Some heterogeneity within meta-analyses; some conflicting reports
- Unclear dose-dependent nature of many of the associated effects


THAT’S NOT ALL…

- Other potential, less well-studied associations with long-term PPIs:
  - Myocardial infarction
  - Iron deficiency
  - Hepatic encephalopathy or spontaneous bacterial peritonitis in cirrhotic patients
  - Small intestinal bacterial overgrowth
  - Fundic gland polyps

QUALITY OF EVIDENCE
- Causality cannot be determined from studies showing the associations discussed
- Amount of evidence vs. lack of randomized controlled trials

Common theme in the literature: reduce inappropriate use of PPIs.

OTHER ROLES FOR THE PHARMACIST
- Be aware of risks associated with use of PPIs, ensure appropriate use and duration
  - H2RAs?
- Tapering of long-term PPIs
  - Rebound acid secretion
  - Tapering strategies may vary

RISKS OF NSAID USE IN OLDER ADULTS

NSAID RISKS
- Gastrointestinal (GI) bleeding
- NSAIDs cause a five-fold increase in fatal peptic ulcer risk
- Risk of peptic ulcer complications is increased within the first month of regular NSAID use
- COX-2 selective NSAIDs have less risk of bleeding complications

BACKGROUND
- 35% of Americans over the age of 50 use aspirin regularly
- 16% of Americans over the age of 50 use other NSAIDs regularly
- NSAID use increased by almost 50% from 2005 to 2010
- NSAIDs are responsible for up to 41,000 hospitalizations and 3,300 deaths each year for seniors in the United States

NSAID COX SELECTIVITY
- Graph showing COX-1 and COX-2 selectivity of different NSAIDs


**NSAID RISKS**

- Renal impairment
  - Increased risk of acute kidney failure in patients with underlying chronic kidney disease
  - More prevalent with long acting NSAIDs


- Cardiovascular risk
  - Increased risk of myocardial infarction and stroke
  - Increased risk of heart failure exacerbation
  - Increased blood pressure


**GI AND BLEEDING RISK**

- Drugs that increase the risk of GI or other bleeding complications with NSAIDs
  - Anticoagulants
  - Antiplatelet agents
  - Corticosteroids
  - Selective serotonin reuptake inhibitors
  - Serotonin and norepinephrine reuptake inhibitors
  - Tricyclic antidepressants
  - Herbal products
    - St. John's Wort
    - Ginkgo Biloba


**KIDNEY RISKS**

- Drugs that increase the risk of kidney injury with NSAIDs
  - Angiotensin converting enzyme inhibitors (ACEI)
  - Angiotensin II receptor blockers (ARB)
  - Antirheumatic agents
    - Methotrexate
    - Diuretics
    - Lithium


**"RENAL FUNCTION TRIPLE WHAMMY"**

- Diuretics reduce plasma volume, reducing glomerular filtration rate
  - ACEIs/ARBs reduce plasma volume, reducing glomerular filtration rate
  - NSAIDs reduce plasma volume, reducing glomerular filtration rate


**NSAIDS IMPEDE ASPIRIN’S ANTIPLATELET ACTIVITY**

- Aspirin is an irreversible inhibitor of the COX-1 enzyme on platelets
  - Aspirin acetylates COX-1, permanently disabling the platelet’s ability to participate in coagulation
  - Cardioprotective benefits are observed with low dose aspirin
  - NSAIDs are reversible inhibitors of COX-1
    - NSAIDs do not permanently inhibit platelet function
    - NSAIDs compete for the binding site of COX-1 with aspirin

TABLE 1: INHIBITION OF ASPIRIN EFFICACY

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Probably</th>
<th>Possibly</th>
<th>Probably Not</th>
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<tr>
<td>Ibuprofen</td>
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<tr>
<td>Celecoxib</td>
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<tr>
<td>Indomethacin</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>All other NSAIDs</td>
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</tbody>
</table>

*Conflicting data: more information needed

OTHER NSAID OBSERVATIONS

- NSAIDs are on the American Geriatric Society Beers Criteria list
- NSAIDs increase the risk of hypoglycemia with oral hypoglycemic agents
- Inhibition of ATP sensitive potassium channels in beta cells may facilitate insulin release
- NSAIDs increase serum lithium levels

OTHER NSAID OBSERVATIONS

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NSAID COUNSELING POINTS

- Use the lowest dose for the shortest duration
- Topical NSAIDs reduce systemic exposure
- Patients requiring NSAIDs with risk factors for GI bleeds should also take a proton pump inhibitor
- COX-2 selective NSAIDs are associated with less bleeding
- Patients using an ACEI/ARB with a diuretic should avoid NSAID use
- Acetaminophen can be used in place of an NSAID for pain relief in these patients

NSAID COUNSELING POINTS

- Patients on aspirin for cardioprotection should avoid NSAID use
- Aspirin should be taken at least 2 hours prior to the NSAID
- Daily NSAID use may prevent aspirin from exhibiting its anti-platelet activity
- Diabetic patients on oral hypoglycemic agents need to be aware of the increased risk of hypoglycemic events when taking NSAIDs
- Patients taking lithium should avoid NSAIDs due to increased risk of lithium toxicity
- Be aware of OTC combination products containing NSAIDs

REFERENCES: CAUTIS
