Patient Safety: Selected Adverse Drug Effects in the Elderly: An Update for 2018

The Schwarting Senior Symposium
Aqua Turf Club
Plantsville, CT
March 29, 2018

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Saint Francis Hospital and Medical Center
Hartford, Ct.

At the conclusion of this knowledge-based activity, the participant will be able to:
• Discuss recent reports of drug-induced electrolyte disorders.
• Describe new ideas for evaluating the adverse drug effect risk of a polymedicine profile using such concepts as stratified risk/benefit drug assessment, drug accumulation ratios, and novel drug burden indexes.
• Explain recent health concerns over the use of iron and zinc supplements.
• Identify recent publications on selected adverse drug effects and drug-drug interactions.

Dennis J Chapron reports no real or potential conflicts of interest relevant to this lecture.

Drug-induced electrolyte disorders

Sodium (mEq/L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>&lt;135</td>
</tr>
<tr>
<td>Normonatremia</td>
<td>135-145</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>&gt;145</td>
</tr>
</tbody>
</table>
Most disorders of sodium involve disorders of water:

Hyponatremia: excess water
Hypernatremia: water loss

Signs and Symptoms of Hyponatremia

- Acute presentation: early (125-130 mEq/L)-nausea and malaise; later (115-120 mEq/L)-headache, lethargy, obtundation, seizures, coma, respiratory arrest.
- Chronic presentation: fatigue, nausea, dizziness, gait disturbance (falls), forgetfulness, confusion, lethargy, muscle cramps

**Hyponatremia**

**Table 1** Hierarchy of outcomes.

<table>
<thead>
<tr>
<th>Hierarchy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically important</td>
<td>Patient survival</td>
</tr>
<tr>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Brain damage/brain oedema</td>
</tr>
<tr>
<td></td>
<td>Epileptic seizures</td>
</tr>
<tr>
<td></td>
<td>Osmotic demyelinating syndrome</td>
</tr>
<tr>
<td></td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Highly important</td>
<td>Bone fractures</td>
</tr>
<tr>
<td></td>
<td>Falls</td>
</tr>
<tr>
<td>Moderately important</td>
<td>Length of hospital stay</td>
</tr>
<tr>
<td></td>
<td>Serum sodium concentration</td>
</tr>
</tbody>
</table>

**Hyponatremia = weakness and confusion**

**American Journal of Medicine, Vol 119, No 1, January 2009**

**CLINICAL RESEARCH STUDY**

Mild Chronic Hyponatremia is Associated with Falls, Unsteadiness, and Attention Deficits

Brecht Kesselsberg, M.D.,* 1 Minh Duc Hoang, M.D.,* Xavier Vandenberghe, M.D.,* Maria L. Mantu, M.D., Ph.D.,* Guy Decuyper, M.D., Ph.D., FACN, FRCP

*The Research Unit for the Study of Hyponatremic Nephropathy, UZ, Erasmus Hospital, Department of Internal Medicine, M.D.

*Nurology Department, Erasmus Hospital, UZ, Brussels, Belgium

**Bone Disease as a New Complication of Hyponatremia: Moving Beyond Brain Injury**

Juan Carlos Ayuso* and Michael L. Motz!* 1

*Bone Consultants of Houston, Houston, Texas; and Division of Nephrology, Children’s Hospital of Pittsburgh at UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Hyponatremia Is Associated With Increased Osteoporosis and Bone Fractures in a Large US Health System Population

Rachel L. Usala, Stephen J. Fernandez, Minhie Phet, Laura Cowen, Navar M. Shaha, Juliana Barsony, and Joseph G. Verbalis

School of Medicine and Graduate School of Arts and Sciences (B.S., U.S.) and Division of Endocrinology and Metabolism (B.S., U.S.), George Washington University, Washington, DC 20007, and Department of Biostatistics and Bioinformatics (I.B., M.M., N.M.S.), George Washington University, Washington, DC 20007

Conclusions: These analyses support the hypothesis that hyponatremia is a risk factor for osteoporosis and fractures. Additional studies are required to evaluate whether correction of hyponatremia will improve patient outcomes. (J Clin Endocrinol Metab 100: 3021-3031, 2015)

Odds of osteoporosis or fragility fractures increase incrementally with categorical decrease in median serum sodium.

Association Between Hyponatremia, Osteoporosis, and Fracture: A Systematic Review and Meta-analysis

Silamir Upala and Anawin Sanguanrueko

Department of Internal Medicine (S.U., A.S.), Benet Medical Center and Columbia University College of Physicians and Surgeons, Cooperstown, New York 13326, and Department of Preventive and Social Medicine (S.U., A.S.), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700 Thailand

“Hyponatremia significantly associates with osteoporosis and fractures. More prospective studies evaluating osteoporosis and fracture risk reduction after hyponatremia correction should be performed.”

(J Clin Endocrinol Metab 101: 1880-1886, 2016)

Table 1. Important Side Effects of Drugs Commonly Prescribed in Older Adults in Primary Care

Prescribing medications, recognizing and managing medication side effects and drug interactions, and avoiding polypharmacy are all essential skills in the care of older adults in primary care. Important side effects of medications commonly prescribed in older adults (statins, proton pump inhibitors, trimethoprim-sulfamethoxazole and fluoroquinolone antibiotics, zolpidem, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, dipeptidyl peptidase 4 inhibitors) were reviewed. Important drug interactions with four agents or classes (statins, warfarin, factor Xa inhibitors, and calcium channel blockers) are discussed. J Am Geriatr Soc 65:1578-1585, 2017.

Table 2. American Geriatrics Society Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults

Antidepressant-Associated Hyponatremia in the Elderly

H. Karl Greenblatt and David J. Greenblatt

Incidences: “… an estimate of 15-20% is reasonably well-supported by available evidence. A more conservative estimate of 5-10% may be justified.”

Journal of Clinical Psychopharmacology • Volume 36, Number 6, December 2016
Antidepressants and the Risk of Hyponatremia: A Class-by-Class Review of Literature

Hyponatremia is a potentially dangerous side effect of antidepressants and is not exclusive to SSRIs. Current evidence suggests a relatively higher risk of hyponatremia with SSRIs and venlafaxine, especially when combined with patient risk factors, warranting clinicians to be aware of this complication. The risks associated with mirtazapine are moderate, supporting this antidepressant as an alternative treatment for patients with an increased risk of hyponatremia.

Effect of Selective Serotonin Reuptake Inhibitors on the Risk of Fracture

Conclusions: Daily SSRI use in adults 50 years and older remained associated with a 2-fold increased risk of clinical fragility fracture after adjustment for potential covariates. Depression and fragility fractures are common in this age group, and the elevated risk attributed to daily SSRI use may have important public health consequences.

Use of Antidepressants and Rates of Hip Bone Loss in Older Women

Conclusions: Use of SSRIs but not TCAs is associated with an increased rate of bone loss at the hip in this cohort of older women.

Association of Low Bone Mineral Density With Selective Serotonin Reuptake Inhibitor Use by Older Men

Conclusions: In this population of men, BMD was lower among those reporting current SSRI use, but not among users of other antidepressants. Further research is needed to confirm this finding in light of widespread SSRI use and potentially important clinical implications.

Drug-Induced Hyponatremia- The 3 Major Offenders

- Serotonin Reuptake inhibitors
- Thiazide diuretics
- Carbamazepine and oxcarbazapine
Approximately 3 in 10 patients exposed to thiazides who continue to take them develop hyponatremia.

Multiple Choice Question

1. All of the following drugs can cause hyponatremia except:
   a. hydrochlorothiazide
   b. citalopram
   c. abiraterone
   d. carbamazepine

Potassium (mEq/L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Normokalemia</td>
<td>3.5 - 5.5</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>&gt;5.5</td>
</tr>
</tbody>
</table>

Signs and Symptoms of Hypokalemia

- Muscle: weakness ascending legs to trunk and arms that can progress to frank paralysis; muscle cramps, rhabdomyolysis, myoglobinuria; respiratory muscle weakness and GI involvement causing ileus
- ECG: ST segment depression, decreased T wave amplitude, increased U wave amplitude, and prolonged QT interval.
- Cardiac arrhythmias: Premature atrial and ventricular beats, sinus bradycardia, junctional tachycardia, AV block, and ventricular tachycardia/fibrillation.
Some Basic Causes of Hypokalemia

1. Increased entry into cells: alkalosis, increased beta adrenergic activity
2. Increased gastrointestinal losses: vomiting, diarrhea, tube drainage
3. Increased renal losses: loop and thiazide diuretics vomiting, mineralocorticoid excess, RTA, tubular damage (aminoglycosides, cisplatin, amphotericin B)

Prevalence of hypokalemia before and after bowel preparation for colonoscopy in high-risk patients

Joana M. de Visser, MD, PhD, Joos A. Heuts, MD, PhD, Effye M. Wyckema, PhD, MD, T. van Diezen, MD, PhD, E. van der Aa, MD, PhD, Hendrik T. van den Berg, MD, PhD, Maastricht, The Netherlands

Background and Aim: Bowel preparation for colonoscopy should not cause significant shifts in serum electrolyte concentrations. We recently encountered 2 cases of severe postcolonoscopy hypokalemia with fatal consequences, prompting us to conduct a study to explore the magnitude of and risk factors for hypokalemia associated with bowel preparation. We paid specific attention to high-risk subgroups, in particular, chronic users, hospitalized patients, and patients estimated to be at high risk by the gastroenterologist.

Conclusions: Hypokalemia is frequently encountered after low-volume polyethylene glycol bowel cleansing in high-risk patients. Additional large-scale studies are needed on the prevalence of hypokalemia in institutionalized populations undergoing bowel cleansing and on the occurrence of potentially very serious side effects in order to advise on screening of high-risk groups in daily clinical practice. (Clinical trial registration number: NTR1185.) (Gastrointest Endosc 2017;86:76-8.)

PEGBP = 2L

The use of diuretic agents is an independent predictor of hypokalemia after a bowel preparation for colonoscopy.

ADEs with short term use of glucocorticoids
Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study

Nearly half (46.9%) of recipients were prescribed a 6-day prepackaged methylprednisolone "dosepak," which tapers the dose from highest to lowest.

Within 30 days of drug initiation, there was an increase in incidence rate of the following:

Sepsis, with an incident rate ratio of 5.30 (95% CI, 3.80 - 7.41);
Venous thromboembolism, with an incident rate ratio of 3.33 (95% CI, 2.78 - 3.99);
Fracture, with an incident rate ratio of 1.87 (95% CI, 1.69 - 2.07).

Disease and Drug Factors that Predispose to Adverse Events with Glucocorticoids

- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Heart failure
- Underlying infection
- Osteopenia or osteoporosis
- Cataract or glaucoma
- Peptic ulcer disease
- Drugs – NSAIDs, warfarin, diltiazem, itraconazole, thiazide and loop diuretics, antidiabetic agents

Effect of Oral Corticosteroids on Chronic Warfarin Therapy
Kathleen A Haywood, Susan E Fugate, and Donald L Harrison

WHAT IS ALREADY KNOWN ON THIS TOPIC
Complications with chronic use of corticosteroids include a wide spectrum of effects on the cardiovascular, musculoskeletal, digestive, endocrine, ophthalmic, skin, and nervous systems.

WHAT THIS STUDY ADDS
This study of 5.5 million privately insured adults (18-64 years) in the US found that one in five patients in an outpatient setting used short term oral corticosteroid over a three year period (2012-14).
Within 30 days of corticosteroid initiation, the incidence of acute adverse events that result in major morbidity and mortality (sepsis, venous thromboembolism, fracture) increased by twofold, to fivefold above background rates.
Greater attention to initiating prescriptions of these drugs and monitoring for adverse events may potentially improve patient safety.

CONCLUSION
One in five American adults in a commercially insured plan were given prescriptions for short term use of oral corticosteroids during a three year period, with an associated increased risk of adverse events.
Example of multi-level DDI with short course glucocorticoid therapy

- 75 yr old man come in contact with poison ivy resulting in severe skin reaction.
- Patient is given short course of methyl prednisone.
- Background drugs include warfarin and diltiazem for atrial fibrillation, metformin with glipizide for type-2 diabetes mellitus.

Multiple Choice Question

2. Short course glucocorticoid therapy has been associated with all of the following except:
   a. somnolence
   b. pulmonary embolism
   c. sepsis
   d. fractures
The Washington Post
Sandra G. Boonman, December 27, 2017

The other big drug problem: Older people taking too many pills

Polypharmacy Definitions

• Polypharmacy - ≥ 5 medications
• Hyperpolypharmacy - ≥ 10 medications
• Extreme polypharmacy - ≥ 20 medications

Trends in Prescription Drug Use Among Adults in the United States From 1999-2012
Elizabeth D. Kantor, PhD, MPH, Colin D. Behm, PhD, MPH, Jennifer S. Huns, MD, MSc; Andrew T. Chan, MD, MPH, Edward L. Giovannucci, MD, ScD

The prevalence of polypharmacy (use of ≥ 5 prescription drugs) increased from an estimated 8.2% in 1999-2000 to 15% in 2011-2012 (difference 6.6% [95% CI, 4.4%-8.2%]; P for trend < .001)

JAMA. 2015;314(17):1818-1831

Polypharmacy is an International Phenomena Community-Dwelling Elderly

• United States - 39%
• Australia – 37.7%
• Germany – 39.1%

Drug Burden Index
[Serum anticholinergic activity]

Diphenhydramine
Paroxetine
Hydroxyzine
Oxybutynin

Clonidine
Desipramine
Citalopram
Nortriptyline
Trazodone
Cyclobenzaprine

Drugs with ACB Score of 1

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
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<tbody>
<tr>
<td>Diphenhydramine</td>
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</tr>
<tr>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td></td>
</tr>
</tbody>
</table>

Drugs with ACB Score of 2

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Symmetrel™</td>
</tr>
<tr>
<td>Belladonna</td>
<td>Multiple</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol™</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Flarin™</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Periact™</td>
</tr>
<tr>
<td>Oxaprine</td>
<td>Loxitane™</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Demerol™</td>
</tr>
<tr>
<td>Methotrimeprazine</td>
<td>Levopromide™</td>
</tr>
<tr>
<td>Molindone</td>
<td>Moban™</td>
</tr>
<tr>
<td>Nefopam</td>
<td>Nefopam®</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Triplast™</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap™</td>
</tr>
</tbody>
</table>
Cumulative Effects Leading to Sedation

- Flexeril
- Zoloft
- Clonidine
- Seroquel
- Ativan
- Requip
- Antivert
- Ultram

Consider other burden indexes

Polypharmacy and Bleeding:
- Gastrointestinal
- Genitourinary

Drug Burden and Bleeding

- Warfarin
- Clopidogrel
- Aspirin
- NSAID
- SSRI
- GC
- DOAC
- INR
- Anti-P
- Anti-P
- Anti-P
- Anti-P
- ?
- CF
- Bleeding

Risk of Upper Gastrointestinal Bleeding From Different Drug Combinations

CONCLUSIONS:

Based on a case series analysis, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRI significant increases the risk of UGIB. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces significant excess risk of UGIB.

Gastroenterology 2014;147:784–792
An 85 year-old man was evaluated in hospital for a fall at home and a resulting hip fracture. He has a past fracture history that includes three spinal compression fractures and a wrist fracture. Past medical history includes GERD for many years, a post stroke seizure 5 years ago, hypertension for 20 yrs, prostate cancer, temporal arteritis, diabetes type II and depression. Medications include lansoprazole 30 mg daily, phenytoin 300 mg daily, furosemide 40 mg daily, nifedipine XL 60 mg, leuprolide depot every 3 months, citalopram 20 mg daily, metformin500 mg bid, pioglitazone 5 mg daily and prednisone 5.0 mg daily.

\[ \Sigma = \text{urinary Ca}^{++} \text{ losses} + \text{GI Ca}^{++} \text{ absorption} + \text{osteoclastic resorption} + \text{osteoblastic activity} \]
Excess Renal Excretion of Calcium
Decreased GI Calcium Absorption
Decreased Estrogen and Testosterone
Decreased Osteoblastic Activity

Furosemide  Lansoprazole  Leuprolide  Prednisone
Prednisone  Prednisone  Citalopram
Phenytoin  Pioglitazone

Drug Burden Index and Potassium Retention

Drug Burden Index

<table>
<thead>
<tr>
<th>Renin Release (D2 cells)</th>
<th>ACE</th>
<th>Adrenal All blockade or decreased aldosterone synthesis</th>
<th>Aldo Receptor or Na Channel Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Valsartan</td>
<td>Spironolactone</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Physiological Systems Compromised by Medications: Potential for Adverse Affects on Gait and Balance

ADE Related Falls Check List

<table>
<thead>
<tr>
<th>Adverse Drug Effects Associated with Falls</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural Hypotension</td>
<td></td>
</tr>
<tr>
<td>Ataxia/parkinsonism or any type of gait/balance problem</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>Muscle/nerve = Weakness</td>
<td></td>
</tr>
<tr>
<td>Dizziness = vestibular</td>
<td></td>
</tr>
<tr>
<td>Impaired Vision</td>
<td></td>
</tr>
</tbody>
</table>

Drug Accumulation

Accumulation ratio = \( \frac{1}{1-e^{-\lambda\tau}} \)

\( \lambda \) = dosing interval
\( -k \) = overall elimination rate constant

Fig 3—Drug concentration in plasma as a function of time during oral drug administration. C = steady state level, with a half-life of 150 hours, a dosage interval of 8 hours, and a systemic availability of 1. C designates the average steady-state concentration.
Benefit- Risk Stratification in Polypharmacy

Rating Drugs According to Selected Characteristics

- Relative efficacy or effectiveness
- Therapeutic Index
- Range of toxicity (mild to severe to fatal)
- Narrow therapeutic range
- Accumulation profile
- Multiple sites of action – primary vs secondary effects
- Degree of interactivity with other co-prescribed medications

Multiple Choice Question

3. Which adverse drug burden would you be concerned about with the following combination of medications: furosemide, omeprazole, prednisone, fluoxetine and pioglitazone?

a. hyperkalemic
b. hyperglycemic
c. hyponatremic
d. osteopenic
Iron and Infections

- Many pathogens require iron in order to mount an infectious assault to human beings.
- As a result the body employs many defensive measures to withhold the availability of iron from an invading pathogen.
- Clinicians unaware of above facts are still giving iron to infected patients while their body is trying to sequester iron from the invading pathogen.

THE ETOLOGY OF THE ANEMIA OF CHRONIC DISEASE AND INFECTION

S. Kent, E. D. Weinbro2 and P. Stewart-Macadam

Abstract—Anemia of infection and chronic disease has traditionally been considered a disorder associated with infections/inflammation. We instead propose that the anemia of infection and chronic disease may be a non-specific immunological defense. We suggest it is analogous to fever, which was also originally considered to be a disorder in need of treatment but which is now seen as a positive response of the host to microbial invasion. We suggest that these two non-specific defenses against microorganism proliferation may have evolved together as complementary strategies the body employs to ward off disease.

Table 2. Microbial genera that contain strains whose growth in body fluids, cells, tissues, and/or intact vertebrate hosts is stimulated by excess iron [15]

<table>
<thead>
<tr>
<th>Gram negative bacteria</th>
<th>Gram positive and Acid-fast bacteria</th>
<th>Fungi and proteozoa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter</td>
<td>Neisseria</td>
<td>Candida</td>
</tr>
<tr>
<td>Aeromonas</td>
<td>Pasteurella</td>
<td>Cryptococcus</td>
</tr>
<tr>
<td>Alcaligenes</td>
<td>Proteus</td>
<td>Enanthema</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>Pseudomonas</td>
<td>Histoplasma</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>Salmonella</td>
<td>Neospora</td>
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<tr>
<td>Escherichia</td>
<td>Shigella</td>
<td>Plasmodium</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Vibrio</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Legionella</td>
<td>Yersinia</td>
<td>Trichomonas</td>
</tr>
<tr>
<td>Moraxella</td>
<td></td>
<td>Trichophyton</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichonosporin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trypanosoma</td>
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J Clin Epi 1994; 47:23

Iron Storage Indices: Novel Predictors of Bacteremia in Hemodialysis Patients Initiating Intravenous Iron Therapy

Curtis B. Johnson, Jr., Daphne B. Eyre, Robert D. Gales, and Bertrand L. Jaffe

Division of Nephrology, University of California, San Francisco, California. Our institution, in common with others, has observed that patients initiating intravenous iron therapy (IVIT) may be at increased risk of bacteremia. We have used a previously published logistic regression analysis to identify the risk factors associated with bacteremia among patients initiating IVIT.

Increased Serum Iron Levels and Infectious Complications after Liver Transplantation

Jennifer K. Giannini, Andrew G. Hesse, Swati Rathore, and David B. Snyder

Department of Medicine, University of California, San Francisco, California. Our study demonstrated that increased serum iron levels were associated with an increased risk of infectious complications in liver transplant recipients. The results of this study suggest that strategies to reduce serum iron levels may be beneficial in reducing the risk of infectious complications after liver transplantation.

Zinc

Zinc is an essential mineral that plays pivotal roles in many aspects of cellular metabolism, such as supporting catalytic activity of approximately 100 enzymes, modulation of immune function, protein synthesis, wound healing, DNA synthesis, cell division, and improvement of intestinal barrier function. Assessment of zinc status in patients is not straightforward because it lacks storage mechanisms and significantly fluctuates with intake. With that in mind, it has been estimated that 15% of IBD patients are affected by zinc deficiency. A recent study showed that zinc deficiency in patients with CD and UC was associated with poor clinical outcomes, increased risk of subsequent hospitalizations, surgeries, and disease-related complications. The investigators showed that these outcomes improve with normalization of zinc and suggested close monitoring and replacement of zinc in IBD patients as needed. Current RDA is 11 mg/d for men and 8 mg/d for women. Zn deficiency is common in patients with IBD, and supplementation may be necessary to achieve normal levels. Certainly, zinc supplementation should be considered in patients with suspected deficiencies.
C. difficile is a spore-forming Gram-positive bacterium that causes a range of gastrointestinal disorders that vary in severity from diarrhea to colitis. The transmissible spore of C. difficile is abundant in healthcare facilities and is resistant to disinfectants, making it a major nosocomial pathogen. The primary risk factor for CDI is antibiotic use, which reduces colonization resistance to C. difficile by altering the gut microbiota. Non-antibiotic-associated and community-acquired CDI cases are increasing, suggesting that other host and environmental factors affect susceptibility to C. difficile. One of the most important environmental factors influencing the gut microbiota, and potentially susceptibility to CDI, is diet. Specifically, dietary metals are associated with susceptibility to numerous infections. Metal availability is a critical factor that affects the outcome of host-pathogen interactions, and metal levels vary widely depending on host diet and environmental exposures. Here we sought to examine the effect of dietary Zn and Zn availability on susceptibility to, and severity of, CDI.

Copper Deficiency Causes Reversible Myelodysplasia

Copper deficiency is a recognized but often overlooked cause of anemia and neutropenia. We began checking serum copper levels on patients referred for evaluation for unexplained anemia and neutropenia or myelodysplasia. Eight patients were identified as copper deficient (serum copper less than 70 μg/dL). The anemia was normochromic and normocytic in seven patients. Neutropenia was present in seven patients. Seven patients had been referred for evaluation of myelodysplasia. Three were seen for consideration for allogeneic stem cell transplant. Five patients had concurrent peripheral neurological symptoms. Seven patients were treated with oral copper gluconate. All treated patients demonstrated a hematological response; seven had a complete remission. The improvement in anemia and neutropenia was rapid with normalization of blood counts within three to four weeks. In one patient, normalization of the underlying marrow dysplasia was demonstrated by bone marrow histology eight months after copper replacement. The cause of copper deficiency was felt to be gastrointestinal malabsorption in five of our patients. We conclude that copper deficiency should be considered in all patients with unexplained anemia and neutropenia or myelodysplasia. Ann. J. Hematol. 82:825-830, 2007. © 2007 Wiley-Liss, Inc.

Zinc – Copper Interaction

Dietary zinc alters the microbiota and decreases resistance to Clostridium difficile infection

Copper

MDS include a heterogenous group of disorders characterized by dysplastic (abnormal) changes within the bone marrow and impaired proliferation of one or more cell lines (erythroid, myeloid and megakaryocytic). It occurs primarily in older men, with a median age of occurrence of 76 yrs.
Copper deficiency

- Hematological disturbances are occur first.
- Neurological disturbances usually proceed the hematological effects.

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Multiple Choice Question

4. Copper deficiency can cause which combination of complications?
   a. gastric ulcers and diarrhea
   b. anemia and myelopathy
   c. dysgeusia and anorexia
   d. dementia and myopathy

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Metabolic Drug-Drug Interactions
A high prevalence of potential drug-drug interactions was found. … which might require intensive monitoring or alternative treatment strategies to prevent suboptimal treatment of co-morbidities in patients treated with Enzalutamide.
Complications of Treatment

The role of drug-drug interactions in prostate cancer treatment: Focus on abiraterone acetate, prednisone, and enzalutamide

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Elderly patients with cancer may have comorbidities, such requiring additional pharmacologic treatment. Therefore, the occurrence of pharmacokinetic (PK) and pharmacodynamic (PD) interactions among drugs is very likely. Consequently, the use of medical therapy for patients with prostate cancer may be compromised by drug-drug interactions. In the treatment of patients with prostate cancer, the use of abiraterone acetate, prednisone, and enzalutamide is common. Drug-drug interactions (DDIs) may occur in prostate cancer patients due to interactions by abiraterone acetate with cytochrome P450 (CYP) enzymes. Abiraterone acetate is metabolized by CYP3A4 and CYP1A2, which are involved in the metabolism of approximately 25% of all drugs, and interaction by enzymes of CYP3A4, CYP1A2, and CYP1A1 which metabolize up to 50% of medications. Therefore, abiraterone acetate may influence plasma levels of CYP3A4- and CYP1A2-metabolized drugs, such as theophylline, ciclosporin, tacrolimus, cyclosporine, and citalopram. Therefore, it is important to consider the potential for DDIs when considering abiraterone acetate treatment.

CYP substrates at risk of abiraterone-DDIs:
- Analgesics (e.g., hydrocodone, codeine)
- Antidepressants (e.g., venlafaxine)
- Cardiovascular drugs (e.g., metoprolol)
- Antidiabetics (pioglitazone)
- Lipid-lowering drug (atorvastatin)

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