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BRIEF REPORT

Iron Absorption in Iron Deficiency Anemia With Alternate-Day Dosing

By Jessica Orner, MD

Family Medicine Physician, Lebanon, PA

Dr. Orner reports no financial relationships relevant to this field of study.

SYNOPSIS: In a cohort of 19 women with iron deficiency anemia, alternate-day doses of iron led to 40-50% more iron absorption compared to consecutive-day doses.

SOURCE: Stoffel NU, Zeder C, Brittenham GM, et al. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica* 2019. pii:haematol.2019.220830. doi:10.3324/haematol.2019.220830.

Researchers in this study evaluated iron absorption in women with iron deficiency anemia using an alternate-day administration. Study participants were recruited from otherwise healthy women participating in a blood donation drive in Switzerland. A cohort of 19 women participated in two study cycles of six days in length, with 16 days between the cycles. The participants were randomly assigned to receive three doses of either 100 mg or 200 mg of ferrous sulfate on days 2, 3, and 5 of the study cycles. If the participant received 100 mg during the first cycle, she received 200 mg during the second and vice versa. The median hemoglobin level was 11.5 mg/dL.

The authors measured iron absorption by labeling the ferrous sulfate with iron isotopes. The doses administered on days 2, 3, and 5 each included a different isotope label. Iron absorption was assessed by measuring isotopic enrichment in red blood cells 16 days after the third dose of ferrous sulfate was administered. Fractional iron absorption was found to be 40-50% higher on day 2 and day 5 compared to day 3 ($P < 0.001$). Absorption on day 2 and day 5 did not differ significantly from each other, meaning that 40-50% more iron was absorbed when there were at least 24 hours between iron doses compared to consecutive days of dosing.

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Stoffel et al also evaluated serum hepcidin levels in relation to iron absorption as a secondary outcome in women with iron deficiency. Hepcidin is the main regulator of iron in the body. High serum hepcidin levels are associated with decreased dietary iron absorption and storage.[1] There is a theory that enterocytes exposed to large doses of iron do not absorb subsequent iron doses over the next five to six days, also known as the "mucosal block" theory. The researchers aimed to evaluate if there was a continued decrease in iron absorption after the serum hepcidin levels tapered that may be linked to decreased enterocyte absorption. In this study, hepcidin levels did increase after iron intake, and those increases persisted for 24 hours. There was not a decrease in iron absorption after 48 hours, which argues against the "mucosal block" theory. From this study, it would be difficult to know if there was any mucosal block in the first 24 hours due to the confounding presence of hepcidin.

While small, this study provides evidence that alternate-day dosing of iron would be beneficial in women with iron deficiency. It showed that they exhibited increased serum hepcidin levels and decreased absorption of iron for at least the first 24 hours after a dose of 100 mg to 200 mg of ferrous sulfate. Based on this information and the information already known about hepcidin's role in iron absorption, clinicians should consider counseling iron-deficient patients to take their iron supplements every other day for better absorption.

While alternate-day dosing of iron may lead to better absorption, there is concern about adherence to an alternate dosing schedule. It would be interesting to see a future study on adherence to this type of schedule to determine efficacy. ■

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BRIEF REPORT

Mortality and Vitamin D Supplementation: A Meta-Analysis

By Jessica Orner, MD

Family Medicine Physician, Lebanon, PA

Dr. Orner reports no financial relationships relevant to this field of study.

SYNOPSIS: In this systematic review and meta-analysis of randomized, controlled trials, researchers determined that when compared with placebo or no treatment, vitamin D supplementation alone was not associated with an increase in overall all-cause mortality, although there were some nuances based on vitamin D form and type of mortality.

SOURCE: Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: Systematic review and meta-analysis. *BMJ* 2019;366:l4673.

Researchers from observation studies have shown an association between low serum vitamin D levels and higher mortality. In this systematic review and meta-analysis of randomized, controlled trials, researchers investigated whether vitamin D supplementation was associated with lower mortality in adults. The researchers conducted an analysis of 52 randomized, controlled trials involving 75,454 participants gleaned from Medline, Embase, and Cochrane Central Register databases from inception through Dec. 26, 2018. Trials excluded from analysis were those including pregnant or lactating women, the critically ill, vitamin D analogs, or in which all participants received vitamin D. For example, if both arms of a study included vitamin D supplementation, that trial was excluded. The analysis focused on vitamin D supplementation vs. placebo or no treatment. If other agents, such as calcium, were given in a trial, the dosage had to be the same in all groups. All-cause mortality was the primary outcome, and

cerebrovascular disease mortality, ischemic heart disease mortality, cancer mortality, cardiovascular mortality, and non-cancer or non-cardiovascular mortality, were the secondary outcomes.

Researchers determined that when compared with placebo or no treatment, vitamin D supplementation alone was not associated with either a positive or negative effect on overall all-cause mortality (risk ratio [RR], 0.98; 95% confidence interval [CI]; 0.95-1.02; I_2 = 0%). However, when evaluating specific types of vitamin D, sub-analyses showed that all-cause mortality was lower in trials with vitamin D_3 (cholecalciferol) than with vitamin D_2 (ergocalciferol) (P for interaction = 0.04). Vitamin D supplementation was associated with a reduction in cancer mortality (RR, 0.84; 95% CI; 0.74-0.95; I_2 = 0%), but only in those receiving vitamin D_3 supplementation. There was no significant reduced risk of cardiovascular mortality, death from cerebrovascular disease, or ischemic heart disease.

Regarding mortality benefits, there is not strong enough evidence to recommend vitamin D supplementation for the general adult population. Vitamins D_2 and D_3 come from different sources, with D_2 mainly coming from plant and some culinary mushrooms, whereas animal sources contain D_3. It appears that if vitamin D has a mortality benefit, it is more likely to be the D_3 form; however, more studies researching that form are needed before changing clinical practice. In this study, researchers did not provide commentary on the role of serum vitamin D levels or whether study participants had known deficiencies, which arguably may be even more important than the form of vitamin D ingested. ■

ABSTRACT & COMMENTARY

2019 Community-Acquired Pneumonia in Adults Guideline: Not Much New Under the Sun

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: The 2019 guideline differs from the 2007 version to only a limited extent.

SOURCE: Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Resp Crit Care Med* 2019;200:e45-e67.

The following is a brief summary of recommendations in the new community-acquired pneumonia (CAP) guideline.

Sputum Gram Stain and Culture, Blood Culture.
It is recommended that these should not be performed routinely in individuals with CAP managed as outpatients. In contrast, it is recommended that these tests be performed in those with severe infection or for whom empiric treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* infection is administered, those with previous infection with one of these organisms, or those who have received parenteral antibiotics while inpatients in the previous 90 days.

Urine Pneumococcal Antigen.
Not routinely recommended, except in severe CAP.

Urine *Legionella* Antigen.
Not routinely recommended, except in those with severe CAP and/or associated epidemiological factors (e.g., in an outbreak or after travel). Culture on selective media or *Legionella* nucleic acid amplification testing also is recommended for those with severe infection.

Influenza Virus Testing.
Rapid influenza nucleic acid amplification testing is recommended when influenza viruses are circulating in the community.

Serum Procalcitonin — Implication for Initiation of Empiric Antibiotic.
Serum procalcitonin results should not affect the decision to initiate empiric antibiotic therapy, which should be administered to all adults suspected to have CAP on clinical grounds and for whom it is radiographically confirmed.

Choosing Outpatient vs. Inpatient Management.
Clinical judgment, together with the Pneumonia Severity Index (PSI) or the CURB-65 tool, should be used to

determine the need for hospitalization. PSI is preferred over CURB-65.

Determining the Level of Inpatient Care.
Direct admission to the ICU is indicated for vasopressor-requiring hypotensive patients and/or those requiring mechanical ventilation because of respiratory failure. In others, clinical judgment, together with use of the 2007 American Thoracic Society/Infectious Diseases Society of America severity criteria, can be used.

Empiric Antibiotic Therapy — Outpatient Management.
In the absence of comorbidities, amoxicillin, doxycycline, or a macrolide may be used, although macrolide monotherapy should be used only in areas where the proportion of pneumococci resistant to this class of agents is < 25%. In patients with significant comorbidities, the recommended choices are amoxicillin/clavulanate or a cephalosporin (cefpodoxime or cefuroxime), each together with a macrolide or doxycycline. Monotherapy with a respiratory fluoroquinolone is an alternative to combination therapy.

Inpatient Empiric Antibiotic Therapy — Absent Risk Factors for MRSA or *P. aeruginosa* Infection.
The preferred regimen for those with nonsevere CAP is either ampicillin/sulbactam, cefotaxime, ceftriaxone, or ceftaroline — each together with a macrolide. Alternatively, monotherapy with levofloxacin or moxifloxacin may be used. Finally, the recommendation for patients with contraindication to both fluoroquinolone and macrolide therapy is one of the beta-lactams listed above together with doxycycline. For patients with severe infection, one of the above beta-lactams, together with a macrolide or a respiratory fluoroquinolone, may be used.

Inpatient Empiric Antibiotic Therapy With Suspected Aspiration Pneumonia — Anaerobic Coverage.
The recommendation is to not routinely add anaerobic coverage in patients with suspected aspiration pneumonia in the absence of a known or suspected empyema or lung abscess.

Inpatient Empiric Antibiotic Therapy — With Risk Factors for MRSA or *P. aeruginosa* Infection.
Empiric coverage for MRSA or *P. aeruginosa* infection is recommended only if locally validated (local prevalence in CAP and local risk factors) are present.

Therapy in the Inpatient Setting — Adjunctive Corticosteroids.
The guideline recommends that neither patients with severe nor nonsevere CAP routinely receive corticosteroids, including those with severe influenza pneumonia. However, the guideline does endorse the recommendation of the Surviving Sepsis Campaign for corticosteroid use in refractory septic shock, defined as unresponsive to fluids and vasopressors.

CAP and Influenza Virus Infection.
Administration of antiviral therapy is recommended for adults with CAP in both the inpatient and outpatient settings, regardless of the duration of illness. Patients in either setting with CAP and influenza virus infection also should initially receive standard empiric antibiotic therapy for CAP.

Duration of Antibiotic Therapy in Adult Outpatients and Inpatients With CAP.
Antibiotic therapy duration is determined by the achievement of clinical stability, as guided by a validated set of criteria and for at least five days.

Follow-Up Chest Imaging.
Follow-up chest imaging is not routinely recommended in patients whose symptoms resolved within five to seven days.

■ COMMENTARY

There are not many significant differences in the 2019 guideline compared to those from the 2007 version. Recommended sputum and blood culture use has been expanded to include not only patients with severe infection, as previously recommended, but also inpatients given empiric treatment for MRSA and/or *P. aeruginosa* infection. Macrolide monotherapy in outpatients without comorbidities should be used only if the local prevalence of resistance is < 25%, a distinction not made in 2007. The category of "healthcare-associated pneumonia" has been eliminated in favor of using local epidemiology and validated risk factors for MRSA or *P. aeruginosa* infection, together with increased emphasis on subsequent de-escalation. For standard empiric therapy of patients with severe CAP, a preference is now expressed for the combination of a macrolide, over a fluoroquinolone, with a beta-lactam. The use of procalcitonin testing to determine the need for antibiotic therapy, adjunctive corticosteroid administration, and/or routine follow-up chest imaging, none of which were discussed in 2007, is not recommended.

One can quibble over a number of the guideline recommendations, but they provide a valuable touchstone for clinical management of patients with CAP, despite the fact that so many of the recommendations are based on low- or very low-quality evidence. Also, the guidelines do not take a stand on two antibiotics, omadacycline and lefamulin, recently approved for the treatment of CAP.

However, overall, it is clear how little we have advanced in our knowledge of the management of adults with CAP in the 12 years since the last version of this guideline. ■

BRIEF REPORT

Think You Don't Smell?

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Fleming A. 'I don't smell!' Meet the people who have stopped washing. *The Guardian,* Aug. 5, 2019. Available at: http://bit.ly/2rqtr5O. Accessed Nov. 8, 2019.

The ecorevolution has spawned some interesting theories and crazy ideas. Not only is there the paleo diet, but also paleo bathing — or, rather, non-bathing. Concerns have been raised that soaps are harmful to the skin, its natural odors, and its natural microbiome, leaving skin open to diseases such as acne, eczema, and even bacterial superinfection. Indeed, certain soaps — and the overuse of hot water — can lead to dry skin and alter its pH.

Not only are a growing number of people forgoing deodorants and soaps, some have gone from washing once a day to once a week or have stopped bathing altogether. Several companies are answering the call for "natural" skin care products intended to restore the normal skin oils and bacteria, including a burgeoning probiotic skin care industry. One French company uses heat-deactivated lactobacillus in a lotion, while another U.S.-based company suspends microorganisms in a gel product.

After watching horses rolling in the dirt, one inventor harvested dirt samples from a local farm, attempted to analyze their function, and concluded that certain strains of bacteria that convert ammonia to nitrogen are necessary for maintaining a pleasant body odor. He created a "Motherdirt" mist spray containing a designated strain of ammonia-oxidizing bacteria to restore natural body odor. Now, there are even "prebiotics," which are intended to nurture the skin's existing microbes.

What is interesting is that many of these nonbathers claim they do not smell. However, our brains literally filter out our own body's odors and its byproducts. That is why the bathroom always smells worse after someone else uses it. Of course, these nonbathers emit an odor; they just do not smell it themselves.

It is true that many mammals and birds survive without a hot shower and instead take "dust baths," the purpose of which has been debated for years. Studies suggest these may be one way to thermoregulate or rid the body of ectoparasites by literally knocking them off or smothering them with dust. Birds may use dust or dirt baths to remove excess oils from feathers so that they are fluffier and provide better insulation. But after watching my chickens roll around in the dirt, I can testify that they are not any cleaner, and they most certainly smell.

Although showering with hot water and harsh soap daily may not be optimal, studies have shown that regular bathing with good soap and water reduces the risk of infection in individuals colonized with *Staphylococcus aureus*. I routinely advise daily baths with a good lye-based soap, a clean washcloth, and lots of sudsing, especially to those areas where bacteria accumulate (axilla, perineum, groin, gluteal crease). With simple hygienic measures and freshly laundered clothing, many patients with methicillin-susceptible *S. aureus* or methicillin-resistant *S. aureus* folliculitis or boils improve. Besides, showers are one of the clear pleasures of the modern world. As the fictional time-traveling Claire Fraser of the *Outlander* series says, in choosing between the attractions of her 23-year-old husband in the 18th century and the benefits of living in the 20th century, hot showers almost won. ■

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BRIEF REPORT

One-Fifth of Adults Have a Food Allergy

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open* 2019;2:e185630.

Are 19% of American adults really allergic to a food? This survey, conducted by the nonpartisan and objective research organization NORC at the University of Chicago from 2015 to 2016, is an extension of a national survey of food allergies conducted in children from 2009 to 2010. The primary outcome measure was the prevalence and severity of a convincing food allergy, based on the presence of at least one symptom on a stringent symptom list in adults in the United States. Food intolerance or symptoms not included in the expert panel's list of stringent symptoms were excluded. The survey was completed by 40,443 adults, with a mean age of 46.6 years.

Remarkably, 19% of adults reported at least one convincing or nonconvincing food allergy. Among adults with a convincing food allergy, nearly half (48%) reported developing at least one food allergy in adulthood, whereas the other half developed their allergy before 18 years of age. Slightly more than half (51%) reported "severe" food allergies, and 45% reported allergies to multiple foods. One-third reported at least one food allergy-related ED visit in their lifetime. Roughly half were told by a physician that they had a food allergy, and one-fourth had filled a prescription for epinephrine at some point.

Women were nearly twice as likely as men to have current food allergies, and twice as likely to have developed a food allergy as an adult. The most common allergies were to shellfish (2.8%), milk (1.9%), peanuts (1.8%), tree nuts (1.2%), and fin fish (0.9%). The prevalence of food allergies did not appear to differ significantly between ethnicities, regions of residence in the United States, or household income.

Interestingly, earlier data suggested that approximately 10.8% of adults would report a food allergy. This would correspond to approximately 26 million adults. Yet, this survey suggests that nearly twice as many people believe they have a food allergy to at least one food, and one-third of them have visited an ED for an allergic reaction to food. That is a lot of ED visits.

There is much to learn about the frequency and consequences of food allergies in adults, which are more common than previously believed. Or, at least a lot of people think they have a food allergy. The obvious question is whether all these people have true food allergies, or just think they do — or, worse, were convinced by a physician that their symptoms are the result of a food allergy, and they are unnecessarily restricting their diet. ■

PHARMACOLOGY UPDATE

Lasmiditan Tablets (Reyvow)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first selective serotonin 1F (5-HT_{1F}) receptor agonist ("ditan") for the acute treatment of migraine headaches.

The drug's selectivity may result in a safer cardiovascular profile than triptans. Lasmiditan is distributed as Reyvow.

INDICATIONS

Lasmiditan is indicated for the acute treatment of migraine with or without aura in adults.[1]

DOSAGE

The recommended dose is 50 mg, 100 mg, or 200 mg taken orally as needed.[1] Lasmiditan is available as 50 mg

and 100 mg tablets. No more than one dose should be taken in 24 hours.

POTENTIAL ADVANTAGES

Lasmiditan provides an alternative to the triptans for acute migraine. Due to the drug's high affinity for the 1F receptor subtype and low affinity for the 1B receptor subtype, lasmiditan does not mediate significant vasoconstriction effects on cerebral or coronary vessels.[2]

POTENTIAL DISADVANTAGES

Lasmiditan is a central nervous system depressant.[1] Patients should not drive or operate machinery for at least eight hours after taking the drug. The most frequent (vs. placebo) adverse events include dizziness (9-17% vs. 3%), sedation (6-7% vs. 2%), paresthesia (3-9% vs. 2%), and fatigue (4-6% vs. 1%).[1] These events were mild or moderate in severity and self-limited.[3] Serotonin syndrome has been reported with lasmiditan in clinical trials.[1] There is a low likelihood (approximately 1%) that lasmiditan could produce euphoria and hallucination. The drug has been approved but is awaiting DEA scheduling before it is made available in the United States. Lasmiditan is an inhibitor of P-gp and breast cancer-resistant protein. Concomitant use with substrates of these transporters should be avoided.[1]

COMMENTS

The efficacy of lasmiditan was evaluated in two randomized, double-blind, placebo-controlled trials.[1,4,5] Investigators enrolled subjects with a history of migraine with and without aura. Study 1 subjects were randomized to lasmiditan 100 mg, 200 mg, or placebo. In study 2, subjects were randomized to 50 mg, 100 mg, 200 mg, or placebo. Efficacy assessments were conducted based on treating migraines with moderate to severe pain within four hours of onset of the attack. The primary efficacy endpoint was the proportion of subjects achieving headache pain freedom and Most Bothersome Symptoms (MBS) at two hours after the first dose of lasmiditan compared to placebo. Pain freedom was defined as a reduction of moderate or severe headache pain to no pain, and MBS was defined as the absence of self-identified symptoms such as photophobia, phonophobia, or nausea. The population for analysis averaged 520 subjects per group.

The percent achieving pain freedom at two hours ranged from 28% to 39% for lasmiditan, compared to 15% to 21% for placebo. MBS success ranged from 41% to 49% compared to 30% to 33% for placebo. Response rates and the time course for onset generally were dose-dependent (i.e., higher dose, greater response rate, and earlier onset of response). Treatment effectiveness was not affected by taking preventive drugs.[7] There is no clear benefit of a second dose as a rescue treatment.[8] In a post-hoc, pooled analysis of these trials, efficacy and safety were evaluated in subjects with one or more cardiovascular risk factors (n = 3,500).[6] The efficacy of lasmiditan was not affected by the degree of CV risk. Treatment-emergent cardiovascular adverse events were numerically higher for lasmiditan than placebo, but not statistically significant (0.9% vs. 0.4%). The most common cardiovascular adverse events were palpitation, tachycardia, and increased heart rate.

CLINICAL IMPLICATIONS

Triptans are considered first-line treatment for acute migraines in adults.[9] However, generally, triptans are 5-$HT_{1B/1D}$ receptor agonists, which mediate vasoconstriction, and many also are 5-HT_{1F} receptor agonists.[2] Lasmiditan is the first "non-vasoconstrictive," central nervous system-penetrating, selective 5-HT_{1F} receptor agonist for treating acute migraine. It may offer a potentially safer alternative to triptans, particularly in patients with cardiovascular history or risk factors (for whom triptans are contraindicated) or those nonresponsive to triptans. Availability is pending DEA action on scheduling. ■

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CME QUESTIONS

1. **The study findings by Stoffel et al support which statement?**
   a. Increased hepcidin levels are associated with better iron absorption.
   b. Daily dosing of iron is more beneficial than alternate-day dosing.
   c. Fractional iron absorption was found to be 40-50% higher during alternate-day dosing.
   d. Increased serum hepcidin levels persist for 72 hours in women with iron deficiency.

2. **In the sub-analysis by Zhang et al, which form of vitamin D was associated with low all-cause mortality?**
   a. Vitamin D_2
   b. Vitamin D analogs
   c. Hydroxylated vitamin D
   d. Vitamin D_3

3. **Which is correct regarding the 2019 American Thoracic Society/Infectious Diseases Society of America guideline for management of community-acquired pneumonia (CAP)?**
   a. Blood culture should be performed routinely in all patients with CAP.
   b. Serum procalcitonin measurement should not be used to determine the need for empiric antibiotic therapy.
   c. All patients with suspected aspiration pneumonia should receive an antibiotic regimen that includes effective coverage of anaerobic bacteria.
   d. Follow-up chest imaging should be performed routinely after five to seven days.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Menopausal Hormonal Therapy and Breast Cancer Risk: Are Old Data Relevant to Today's Practice?

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