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Clin Gastroenterol Hepatol 2018 May 22

Low Quality and Readability of Internet Dietary Information on Irritable Bowel Syndrome

Clinicians should counsel patients seeking online dietary help for IBS accordingly.

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal diagnoses, and diet plays an important role in its management. Patients often use the Internet as a primary source for health information, including dietary advice. However, previous studies show significant variation in the quality of websites focused on inflammatory bowel disease (Inflamm Bowel Dis 2009; 15:1891) and colorectal cancer screening (Clin Gastroenterol Hepatol 2017; 15:79).

Using validated instruments for assessing website quality and readability, researchers surveyed websites specialized in dietary recommendations in IBS. They found low reliability, information quality, and overall quality for 24 pediatric IBS websites and moderate reliability and overall quality but low information quality for 29 adult IBS websites. High-fiber diet was most commonly recommended, followed by low-FODMAP diet. Readability was rated as difficult for both pediatric and adult IBS sites.

COMMENT: Most clinical gastroenterologists have experienced the situation where patients walk into clinic with a printout they obtained from the Internet regarding their ailment or proposed remedy. Websites focused on gastrointestinal disorders abound and often influence patient decision making. This study is an additional cautionary note that such information can be of marginal quality and difficult to understand and that physicians should counsel their patients accordingly.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Cruz LA et al. Assessment of quality and readability of Internet dietary information on irritable bowel syndrome. Clin Gastroenterol Hepatol 2018 May 22; [e-pub]. (<https://doi.org/10.1016/j.cgh.2018.05.018>)

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JAMA Pediatr 2018 May 29

Vitamin D Supplementation in Pregnancy May Benefit Infants

A meta-analysis showed multiple benefits, including a lower risk for being small for gestational age.

Vitamin D supplementation during pregnancy has been studied repeatedly to determine its effects on child health outcomes. Results have varied, prompting this meta-analysis of data from 24 randomized, controlled trials of prenatal vitamin D supplementation including 5400 participants. Although supplement doses and dosing frequencies varied widely among included trials, intervention group doses averaged at least 400 international units (IU) daily.

Multiple outcomes were analyzed, with the following notable findings:

- Prenatal vitamin D supplementation was associated with:
 - Lower risk for newborn being small for gestational age (SGA)
 - Increased neonatal 25(OH)D and calcium levels
 - Increased weight at birth and at 3, 6, 9, and 12 months
 - No increase in neonatal mortality or congenital abnormality
 - No difference in risk for asthma, eczema, respiratory infections, or allergies
- Lower vitamin D doses (≤ 2000 IU/day) were associated with lower mortality, while higher doses (> 2000 IU/day) were not.
- Timing of supplementation (< 20 weeks vs. ≥ 20 weeks gestation) was not associated with risk for SGA or neonatal mortality.

COMMENT: Prenatal vitamin D supplementation typically would fall under the purview of obstetricians, family practitioners, and others caring for pregnant women, but these data remind us to encourage women we see in our practices to ask their prenatal care providers about vitamin D. It is becoming apparent that vitamin D both before and after birth can positively affect child health, and we are in a position to advocate for early exposure for our patients-to-be.

CITATION(S): Bi WG et al. Association between vitamin D supplementation during pregnancy and offspring growth, morbidity, and mortality: A systematic review and meta-analysis. JAMA Pediatr 2018 May 29; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2018.0302>)



Blood Adv 2018 May 8; 2:969

Does Vitamin D Prevent Respiratory Complications in Children with Sickle Cell Disease?

In a randomized trial, respiratory illnesses decreased by over 50% in children receiving monthly, oral vitamin D supplementation for 2 years.

Vitamin D's immunomodulatory effects may decrease the risk for respiratory illness and infections. To examine this potential benefit in children with sickle cell disease, researchers randomized 62 patients to receive a monthly, oral high dose (100,000 IU) or standard dose (12,000 IU) of vitamin D for 2 years in a double-blind trial. Participants' age range was 3 to 20 years.

Overall, receipt of monthly oral vitamin D was associated with a reduction of over 50% in the rate of respiratory illnesses during the second year, with similar decreases in each treatment group. Annual rates of respiratory events were also similar between groups. At baseline, the mean 25-hydroxyvitamin D level was in the deficient range at 14.3 ng/mL for the total sample. The standard-dose group stabilized at a mean concentration of 19.3 ng/mL, which is still deficient, while the high-dose group stabilized at 37.0 ng/mL.

COMMENT: In this first randomized trial of vitamin D for this indication, the decrease in the rate of annual respiratory events by year two was striking. However, this finding cannot be completely ascribed to the intervention in the absence of a placebo group. These data lend support to the use of empiric vitamin D supplementation for these patients, who have frequent clinic visits. Clinicians might also consider observed administration of a bolus in clinic if there are concerns for daily adherence. Studying whether the same findings hold after daily, lower-dose vitamin D supplementation would be a next step, extending the findings to typical at-home practices. This simple intervention could have profound implications for reducing morbidity and mortality in these high-risk patients.

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CITATION(S): Lee MT et al. Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease. Blood Adv 2018 May 8; 2:969. (<https://doi.org/10.1182/bloodadvances.2017013979>)

JAMA Pediatr 2018 May 29

Higher Vitamin D Dosage Does Not Improve Infant Outcomes

Bone strength and infection frequency were similar with 400 and 1200 IU/day vitamin D₃ supplementation in infants.



Because vitamin D is known to play key roles in bone mineralization and immune function, researchers in Finland examined whether higher-than-standard-dose vitamin D₃ supplementation in infants improves bone strength or reduces infection frequency. They randomized 975 infants to receive either standard-dose (400 IU) or high-dose (1200 IU) vitamin D₃ daily from age 2 weeks to 24 months. Bone strength was assessed at 24 months using peripheral quantitative computed tomography. Parents reported infection frequency in diaries assessed at 6, 12, and 24 months.

Almost all infants were vitamin D-sufficient at birth (96%) and at 24 months (99%). No infants showed signs of vitamin D toxicity. Neither bone strength measures nor infection frequency differed between groups at any time point.

COMMENT: While 1200 IU/day of vitamin D appears to be safe, it did not provide added benefit for bone strength or infection risk in infants who were vitamin D-sufficient at birth. This study does not help us understand optimal dosing for populations with a higher rate of vitamin D deficiency. Clinicians who work with such populations should be alert for new studies assessing effects of higher-than-standard infant supplement dosing among the vitamin D-deficient.

CITATION(S): Rosendahl J et al. Effect of higher vs standard dosage of vitamin D₃ supplementation on bone strength and infection in healthy infants: A randomized clinical trial. JAMA Pediatr 2018 May 29; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2018.0602>)

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American College of Obstetricians and Gynecologists. Obstet Gynecol 2018 May 17

Staying on Top of Postpartum Pain

Maximizing nonopioid approaches to managing pain during the early postpartum period.

Sponsoring Organization: American College of Obstetricians and Gynecologists (ACOG)

Target Population: Obstetric and women's healthcare providers

Background and Objective: Approaches to managing postpartum pain vary widely throughout the world. With the goal of improving and standardizing management practices in the U.S., ACOG, the American College of Nurse Midwives, and the American Academy of Family Physicians jointly developed a guideline.

Key Recommendations

- Follow an individualized, stepwise approach to postpartum pain management.
- Whenever possible, encourage nonpharmacologic options first:
 - Breast engorgement: cold packs, increased frequency of breast-feeding
 - Nipple pain: apply breast milk to nipple; use breast shield
 - Uterine cramps: heating pad
 - Perineal pain: ice packs, cold gel packs
- Promote use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.
- Prescribe opioids only if the highest allowable doses of NSAIDs (e.g., ibuprofen 400 mg every 4 hours; maximum daily dose, 3200 mg) and acetaminophen (650 mg every 4 hours; maximum daily dose, 3250 mg) fail to provide sufficient pain relief.
- Consider alternating NSAIDs and acetaminophen every 4 hours.



- Intravenous ketorolac (30 mg every 6 hours), albeit effective, should not be given to women with allergies to ketorolac or aspirin, renal dysfunction, or a bleeding diathesis.
- If opioids are prescribed at discharge, limit the number of doses and provide education about safe disposal of unused tablets.
- The FDA recommends against prescribing codeine or tramadol for breast-feeding women. (Pharmacogenetic differences in *CYP2D6* may cause rapid metabolism to morphine, which may enter breast milk in excessive quantities).

COMMENT: In a large study involving opioid-naive women with cesarean deliveries, 1 in 300 became persistent users of opioids during the first postpartum year — and factors that raised this risk included past use of cocaine or other recreational drugs, tobacco use, history of back pain or migraines, and use of antidepressants or benzodiazepines (*Am J Obstet Gynecol* 2016; 215:353.e1). Clearly, excessive administration of opioids for postpartum pain represents a major deficiency in U.S. clinical practice. Our protocols have been based on teachings from an outdated generation of clinical authorities. Only scant evidence from randomized trials demonstrates that opioids are better than NSAIDs for postpartum pain. In the U.K., women and their clinicians typically manage such pain without routinely turning to opioids (see NICE Guideline). We can learn from their best practices, thereby minimizing our reliance on opioids to treat women with this multifaceted condition.

CITATION(S): American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 742: Postpartum pain management. *Obstet Gynecol* 2018 May 17; [e-pub]. (<https://doi.org/10.1097/AOG.0000000000002683>)

Obstet Gynecol 2018 Jun; 131:1095.

Does Endometriosis Raise Risk for Developing Ovarian Cancer?

Yes, especially the ovarian subtype of endometriosis (i.e., endometrioma); however, absolute risk for ovarian cancer remained low.

To investigate the relation between various types of endometriosis and risk for ovarian cancer, Finnish investigators used nationwide data in a study of some 50,000 women with surgically confirmed endometriosis diagnosed between 1987 and 2012 (follow-up, 839,000 women-years). Endometriosis subtypes included ovarian, peritoneal, and deep infiltrating.

Compared with women who did not have endometriosis, those with the condition were at significantly higher risk for developing ovarian cancer (standardized incidence ratio [SIR], 1.8) although absolute risk for ovarian cancer remained low (approximately 2 additional cases of ovarian cancer per 10,000 women years of follow-up). The magnitude of the association varied for different ovarian cancer types (clear cell SIR, 5.2; endometrioid SIR, 3.2; serous SIR, 1.4; mucinous SIR, 0.9). The ovarian subtype of endometriosis (i.e., endometrioma) was associated with the highest risk for ovarian cancer (SIR, 2.6), particularly clear cell (SIR, 10.1) and endometrioid (SIR, 4.7) ovarian cancer. Isolated peritoneal endometriosis was associated with slightly increased risk for ovarian cancer that did not reach statistical significance (SIR, 1.3).

COMMENT: In the U.S., endometriosis has been diagnosed in about 8% of women aged 15 to 45. This study helps to clarify that women with ovarian endometriosis — but not peritoneal endometriosis — are at increased risk for ovarian cancer (although longer follow-up in a larger cohort is required to clinch this finding). Some ovarian endometriosis lesions harbor genetic changes (e.g., *ARID1A* mutations) that may also occur in ovarian cancers. In the future,



molecular analysis of ovarian endometriosis specimens might help to identify those women at highest risk for developing ovarian malignancies.

CITATION(S): Saavalainen L et al. Risk of gynecologic cancer according to the type of endometriosis. *Obstet Gynecol* 2018 Jun; 131:1095. (<https://doi.org/10.1097/AOG.0000000000002624>)

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Obstet Gynecol 2018 May; 131:e124

Endometrial Evaluation in Women with Postmenopausal Bleeding

ACOG continues to recommend transvaginal ultrasound as an initial assessment.

Sponsoring Organization: American College of Obstetricians and Gynecologists (ACOG)

Target Population: Women's healthcare providers

Background and Objective: Although postmenopausal vaginal bleeding is common — and endometrial cancer is the most common gynecologic malignancy in U.S. women — the great majority of women with postmenopausal bleeding do not harbor uterine neoplasia. Nonetheless, prompt initial evaluation is important.

Key Recommendations

- Transvaginal ultrasound (TVUS) is appropriate for initial evaluation of postmenopausal bleeding. If the endometrium has a sonographically measured thickness ≤ 4 mm, further evaluation might not be necessary. If bleeding persists or recurs, endometrial sampling is indicated.
- Obesity, uterine position, or myometrial abnormalities may preclude satisfactory endometrial assessment with TVUS. In these cases, postmenopausal bleeding should be evaluated with sonohysterography, office hysteroscopy, or endometrial sampling. If such sampling yields insufficient tissue for diagnosis, further evaluation might not be necessary, provided subsequent TVUS demonstrates an endometrial thickness ≤ 4 mm and bleeding does not recur.
- When postmenopausal women without bleeding undergo TVUS for indications such as pelvic pain or adnexal pathology, an endometrial thickness >4 mm may be incidentally found. In this setting, additional endometrial assessment is not routinely indicated (although patient-specific factors and imaging findings may warrant further evaluation).

COMMENT: Optimal evaluation of women with postmenopausal bleeding should identify the small proportion who have endometrial neoplasia while minimizing the use of invasive procedures in those with benign causes of such bleeding. These guidelines should help clinicians reach this goal.

CITATION(S): American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 734: The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstet Gynecol* 2018 May; 131:e124. (<https://doi.org/10.1097/AOG.0000000000002631>)



JAMA 2018 May 22; 319:2095

Intensive Surveillance for Colorectal Cancer

More- versus less-frequent testing did not improve survival after curative treatment for patients with stage II–III disease.

How often to perform surveillance testing after curative treatment for patients with stage II–III colorectal cancer (CRC) remains controversial, as guidelines support varying intensity of screening, including follow-up imaging with computed tomography (CT) scan, testing of serum carcinoembryonic antigen (CEA), and colonoscopy.

Investigators now report the results of an international, randomized trial (COLOFOL) that evaluated two surveillance testing strategies following curative surgery for stage II–III CRC. A total of 2365 per-protocol patients (median age, 65) were randomized to high-frequency testing (CT scan of the chest and abdomen and CEA at 6, 12, 18, 24, and 36 months) or low-frequency testing (CT scan and CEA at 12 and 36 months). Colonoscopy and pelvic imaging were allowed at the discretion of the treating physician. Among the patients, 35% to 37% had rectal cancer, 46% to 48% received adjuvant chemotherapy, and 53% to 54% had stage II CRC. The coprimary endpoints were 5-year mortality and 5-year disease-specific mortality.

At median follow-up of 5 years, 5-year mortality was similar with high-frequency or low-frequency screening (13.3% and 14.5%, respectively), as were 5-year disease-specific survival (10.8% and 11.7%) and disease recurrence (22.1% and 19.8%).

COMMENT: These findings are consistent with data from other trials that indicate that less-frequent CT imaging and CEA testing is appropriate after curative treatment for stage II–III CRC and should be considered in the development of treatment guidelines.

CITATION(S): Wille-Jørgensen P et al. Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: The COLOFOL randomized clinical trial. JAMA 2018 May 22; 319:2095. (<https://doi.org/10.1001/jama.2018.5623>)

Sanoff HK. Best evidence supports annual surveillance for resected colorectal cancer. JAMA 2018 May 22; 319:2083. (<https://doi.org/10.1001/jama.2018.5817>)

Mult Scler 2018 May 1

Does “No Evidence of Disease Activity” at 2 Years Predict 16-Year MS Outcomes?

Radiologic activity did not predict disease progression.

Setting treatment goals in multiple sclerosis (MS) and defining thresholds for suboptimal response have been hot topics. The formulation ‘no evidence of disease activity’ (NEDA) encompasses clinical findings (freedom from relapses, disability progression) as well as radiologic ones (new lesions on MRI).

The interferon-beta 1b studies from the mid-1990s recruited 376 patients with active MS and randomized them to treatment or placebo. Investigators evaluated patients who had NEDA at 2 years for negative disability outcomes

(NDOs) at 16 years. (Negative outcomes included death, need for wheelchair, and transitioning to secondary progressive disease.)

At 16 years, 245 of the 376 trial participants were assessed. An NDO was present in 129 patients (53%). For patients who had achieved clinical NEDA at 2 years (18%), the likelihood of experiencing an NDO was decreased by 84%. However, adding MRI outcomes to clinical evidence of NEDA did not increase predictive accuracy for NDOs.

COMMENT: A limitation of this study is that patients were not treatment-escalated by a protocol in response to not achieving NEDA. The current data support the idea that three to five new T2 lesions and one or two new gadolinium lesions are associated with an increased risk for worsening future disability. Early disability progression and one or two early relapses should signal a concern for increased risk of long-term disability.

CITATION(S): Goodin DS et al. Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b. *Mult Scler* 2018 May 1; [e-pub]. (<https://doi.org/10.1177/1352458518773511>)

Lancet Neurol 2018 Jun; 17:539

Impact of Microbleeds on Anticoagulation-Related Bleeding After Stroke

In patients with atrial fibrillation and stroke, cerebral microbleeds identified on acute MRI after a stroke were associated with increased risk for intracerebral hemorrhage in the 2 years after post-stroke anticoagulation initiation.

Cerebral microbleeds can be detected on brain MRI using sequences such as susceptibility-weighted imaging. Microbleeds are thought to represent small-vessel vasculopathy and are often found in patients with poorly controlled hypertension or cerebral amyloid angiopathy (CAA). Microbleeds can also be associated with cognitive impairment. For patients with atrial fibrillation (AF) who require oral anticoagulation medication after ischemic stroke, does the presence of microbleeds alter the risk/benefit ratio? To find out, researchers recruited patients with AF and a recent stroke or transient ischemic attack at 79 European centers and tracked outcomes for 24 months. The primary outcome was symptomatic intracranial hemorrhage (ICH).

Of 1490 patients (mean age, 76; 58% men), 1447 patients had follow-up data available, of whom 311 had at least 1 microbleed (median number, 1). The microbleed was strictly lobar in 116 patients, exclusively deep in 120, and mixed in 75. Only 3% of participants met the criteria for CAA. During follow-up, the rate of symptomatic ICH was 9.8 per 1000 patient-years in patients with microbleeds, compared with 2.6 per 1000 patient-years in patients without microbleeds (adjusted hazard ratio, 3.7). Compared with the HAS-BLED score alone, using information about microbleeds in addition to HAS-BLED score improved the prediction of ICH. More patients with than without an ICH had started a vitamin K antagonist after the ischemic event (86% vs. 62%).

COMMENT: This study provides evidence that a neuroimaging biomarker of small vessel vasculopathy can be useful in the prediction of future ICH events. However, the risk for embolic stroke will still likely outweigh the risk for ICH for the vast majority of AF patients. In addition, with the increasing use of novel oral anticoagulation medications, one would expect the ICH rate to be lower in the future.

CITATION(S): Wilson D et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): A multicentre observational cohort study. *Lancet Neurol* 2018 Jun; 17:539. ([https://doi.org/10.1016/S1474-4422\(18\)30145-5](https://doi.org/10.1016/S1474-4422(18)30145-5))



N Engl J Med 2018 Jun 7; 378:2182

Five-Year Stroke Risk After Transient Ischemic Attack or Minor Stroke

Half of the 13% risk accrues within the first year; the other half accumulates over the next 4 years.

In recent decades, reductions in stroke and cardiovascular events after transient ischemic attack (TIA) and minor stroke have occurred as a greater appreciation of the risk, the development of validated methods to stratify this risk, and the development and implementation of systems of care and acute interventions to modify this risk. Studies from 1997 to 2003 estimated that the 3-month risk for stroke or acute coronary syndrome after TIA or minor stroke was between 12% and 20%. But a more recent large multinational study put the 1-year risk at 6.2% (N Engl J Med 2016; 374:1533).

Now, these same investigators (TIAregistry.org) report 5-year outcomes for 3847 patients enrolled at the 42 sites where 5-year outcomes data were available for more than 50% of enrollees (80% of the original cohort).

The risk for stroke, acute coronary syndrome, or death from cardiovascular causes was 6.4% in the first year and 6.4% over the next 4 years. As in the previous study, large-artery atherosclerosis, cardioembolism, and baseline ABCD² score were each associated with increased stroke risk, but the presence of a lesion on neuroimaging which had been associated with 1-year risk, was not associated with 5-year risk.

COMMENT: The outcomes from sites participating in this registry may not be representative of outcomes from other regions or countries without similar follow-up and without similar demonstrated interest in systematically capturing data on TIA patients. But that half of the cardiovascular risk persists after 1 year even among these highly motivated sites could raise the stakes for ensuring a more seamless transition from short-term to long-term secondary prevention efforts.

CITATION(S): Amarenco P et al. Five-year risk of stroke after TIA or minor ischemic stroke. N Engl J Med 2018 Jun 7; 378:2182. (<https://doi.org/10.1056/NEJMoa1802712>)
