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Scand J Gastroenterol 2019 Oct 19

An Increasing Proportion of Peptic Ulcers Are Idiopathic

Meanwhile, Helicobacter pylori ulcers are becoming less common.

The major risk factors for peptic ulcer disease remain *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Although a variety of less common causes are associated with peptic ulcers, including Zollinger-Ellison syndrome, smoking, and severe illness, there is an increasingly prevalent category with no obvious etiology called idiopathic peptic ulcer disease (IPUD). Despite its increasing importance, IPUD is poorly understood.

To better understand the prevalence and risk factors associated with IPUD, investigators in Italy retrospectively studied the medical records of 9212 patients undergoing upper endoscopy from 2002 to 2018.

Among 380 patients with peptic ulcer disease, the proportion of those with IPUD steadily increased (from 20% before 2005 to 51% after 2015), whereas the proportion of those with *H. pylori* steadily decreased. Most IPUD ulcers (80%) were located in the stomach, 13% were in the duodenum, and 7% of patients harbored multiple ulcers. Risk factors for

IPUD in a multivariable analysis were history of prior peptic ulcer disease (odds ratio, 3.73), age >60 (OR, 3.52), male sex (OR, 3.13), hospitalization (OR, 2.97), and use of multiple (\geq 4) medications (OR, 2.81).

COMMENT: Patients with IPUD represent an increasing percentage of those with peptic ulcers. After exclusion of *H. pylori* infection and NSAIDs as causes, more unusual causes must be excluded. For the remaining ulcers without obvious etiology, causes are likely to be multifactorial. More work is required in larger patient populations to understand the contributing factors before the etiology of these ulcers is no longer idiopathic.

Ann Intern Med 2019 Oct 15

Intervention for Aggression and Agitation in Dementia

Which is better for treating aggression and agitation in dementia, nonpharmacologic or pharmacologic interventions?

Neuropsychiatric symptoms in those with dementia can be challenging to treat. Researchers conducted a systematic review and network meta-analysis of 163 randomized, controlled trials to compare the effects of nonpharmacologic and pharmacologic interventions on aggression and agitation in those with dementia.

Most studies had a mean patient age of ≥70 years, at least 50% women, and a duration of less than 11 weeks. Of the included studies, dementia type was not specified in 37% and 28% focused on Alzheimer disease. Dementia severity was not reported in 43% of the studies, mild/moderate/severe dementia was included in 27% of the studies, and moderate/severe dementia was the focus in 20% of the studies.

For physical or verbal aggression, modification of activities of daily living (ADL) or massage and touch therapy was more efficacious than usual care, antipsychotics, and/or caregiver education. Outdoor activities were also more efficacious than the other modalities for physical aggression. Massage and touch therapy were more efficacious than usual care or caregiver education for physical agitation. No intervention was effective for verbal agitation. For combined aggression and agitation, recreation therapy, multidisciplinary care, and massage and touch therapy with or without music were more efficacious than usual care.

COMMENT: Nonpharmacologic treatments should be prioritized when treating agitation and aggression in patients with dementia, although one limitation of the analysis is that most of the studies did not address violent aggressive behavior. If agitation and aggression occur acutely in a patient with dementia, it is also important to look for underlying medical issues such as an infection, recent stressors, or environmental changes that may have triggered the behavior.

Peanut Oral Immunotherapy for Peanut Allergy

Oral immunotherapy produces temporary desensitization in most patients but does not cure peanut allergy.

Studies have shown that oral immunotherapy (OIT) is effective at desensitizing patients to peanut allergen, but we don't know whether this can lead to permanent tolerance. Researchers in California enrolled 120 children and adults (age range, 7–55) with peanut allergies to test the long-term effectiveness of peanut OIT.

Patients were randomized to one of three groups:

- Build-up dosing to achieve 4000 mg of peanut powder (≈14 peanuts) daily for 2 years, then switch to placebo (oat flour) daily for 1 additional year
- Build-up dosing to achieve 4000 mg of peanut powder daily for 2 years, then switch to 300 mg of peanut powder (≈1 peanut) daily for 1 additional year
- Placebo for 3 years

In the two active groups, 85% of patients passed a 4000-mg oral challenge at 2 years, compared with just 4% of control patients. However, during the months after stopping OIT, most patients gradually lost their ability to consume large amounts of peanut protein.

COMMENT: On September 13, 2019, an FDA advisory committee recommended approval of a peanut OIT. If this OIT is approved, peanut-allergic patients will have to make a difficult decision, because a recent meta-analysis showed that patients who are receiving OIT actually experience more allergic reactions and have excess risk for eosinophilic esophagitis than do patients who avoid peanuts (NEJM JW Gen Med Jun 1 2019 and Lancet 2019; 393:2222). And now, these findings suggest that patients might have to continue OIT indefinitely to maintain their desensitization.

CITATION(S): Chinthrajah RS et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): A large, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2019 Sep 12; [e-pub]. (https://doi.org/10.1016/S0140-6736(19)31793-3)

Psychol Med 2019 Sep 19

Support for Fish Consumption During Pregnancy

In a large observational study in Japan, higher fish intake during pregnancy was associated with better postpartum mental health.

Given the substantial maternal and neonatal morbidity associated with postpartum depression, effective interventions are critical. Randomized controlled trials (RCTs) of n-3 polyunsaturated fatty acids (PUFAs) for depression during pregnancy have yielded mixed results; studies using higher PUFA doses showed greater benefit but had smaller sample sizes. RCTs of PUFAs for preventing postpartum depression are lacking — and it's unclear whether intake of fish or PUFAs is more important.

Researchers for the Japan Environment and Children's Study evaluated 6- and 12-month postpartum outcomes in 84,181 and 81,924 pregnancies, respectively. Self-reported fish consumption during mid and late pregnancy was assessed, and

both fish and PUFA intake were stratified into quintiles (median daily fish intake by quintile was 5 g [lowest] and 69 g [highest]).

Overall, 11.6% of women had postpartum depression at 6 months, and 2.6% had serious mental illness at 12 months. In adjusted analyses, reduced risks for postpartum depression at 6 months and serious mental illness at 12 months were observed for the four highest quintiles versus the lowest quintile of fish and PUFA intake during pregnancy.

COMMENT: These results suggest that increasing intake of fish and dietary PUFAs could help prevent postpartum mental health problems. In light of previous mixed data, this report highlights the need for more interventional studies focusing on the effects of dietary fish as opposed to fish oil supplements, while establishing optimal PUFA doses (as only patients in the lowest quintile seemed to have inadequate PUFA). For now, women with a history of depression could consider eating more fish or taking fish oil supplements during pregnancy if deemed safe by their clinicians.

CITATION(S): Hamazaki K et al. Dietary intake of fish and n-3 polyunsaturated fatty acids and risk of postpartum depression: A nationwide longitudinal study - the Japan Environment and Children's Study (JECS). *Psychol Med* 2019 Sep 19; [e-pub]. (https://doi.org/10.1017/S0033291719002587)

https://jamanetwork.com/journals/jamapediatrics/article-abstract/2754101

Could Too Much Screen Time Change Preschoolers' Brain Structure?

By Amy Orciari Herman Edited by David G. Fairchild, MD, MPH, and Jaye Elizabeth Hefner, MD

Preschoolers who spend too much time in front of screens show differences in brain development that could affect language and reading skills, suggests a cross-sectional study in *JAMA Pediatrics*.

Nearly 50 healthy children aged 3 to 5 years underwent cognitive testing and brain magnetic resonance imaging, while their parents completed questionnaires about their screen-based media use.

Children with higher screen time scores had lower scores on some cognitive tests, but these associations were no longer statistically significant after adjustment for household income. However, MRI revealed that children with higher screen scores had lower microstructural integrity of brain white matter tracts that are involved in early language and literacy development — a finding that persisted after adjustment.

Dr. Jenny Radesky of *NEJM Journal Watch Pediatrics and Adolescent Medicine* weighs in: "These findings are fascinating but very, very preliminary. This study is cross-sectional and therefore doesn't prove causality. Like all media research, we need to study children over time to observe interactions between their innate characteristics and their media use. For example, do children with developmental differences (e.g., early ADHD) who may have a particular white matter phenotype happen to prefer or demand more media use, or is media use influencing white matter development?"

Pediatric Advice Linked with Safer Infant Sleep Practices

High geographic and demographic variation in unsafe sleep behaviors suggests an opportunity for improvement.

Sudden unexpected infant death (SUID) is the most common cause of infant mortality and is extremely traumatic for families. Although rates of SUID have decreased since the 1990s, the practice of bed-sharing has increased during this time, and more than half of nighttime caregivers still report using soft bedding. To examine use of safe infant sleep practices in the U.S., researchers analyzed data from mothers in 29 states who participated in the 2016 Pregnancy Risk Assessment Monitoring System at 2 to 9 months postpartum.

Most mothers reported putting infants to sleep on their backs (78%), but fewer stated that they room-shared without bed-sharing (57%), avoided soft bedding materials such as blankets and pillows (42%), and always or often used a separate approved sleep surface (32%). Having the infant occasionally sleep on a couch or armchair, which increases suffocation risk, was reported by 9% of mothers. Rates of unsafe sleep practices varied widely between states (by as much as 20%) and also varied between sociodemographic groups. Non-Hispanic black mothers, American Indian/Native American mothers, and smokers — all groups with higher rates of SUID — showed particularly elevated rates for some unsafe sleep practices. Mothers who reported receiving advice from a pediatric clinician were 12% to 28% more likely to report safe infant sleep practices.

COMMENT: Infant sleep practices are heavily influenced by social norms. Changing norms is difficult, especially with exhausted new parents who may be bombarded with parenting recommendations from the Internet and social media. The fact that recalling safe sleep advice was associated with healthier infant sleep practices should reassure pediatric clinicians that they have a chance to influence safe sleep norms, especially within the context of a trusted relationship.

CITATION(S): Hirai AH et al. Prevalence and factors associated with safe infant sleep practices. *Pediatrics* 2019 Oct 21; [e-pub]. (https://doi.org/10.1542/peds.2019-1286)

Circulation 2019 Sep 30

Are Patients with Short-Duration Atrial Fibrillation at Risk for Stroke?

Patients with device-detected AF durations between 5 minutes and 24 hours and CHA₂DS₂-VASc scores of 3 and higher would probably benefit from anticoagulation.

Despite questions about the accuracy of CHA₂DS₂-VASc, it is useful for predicting which patients with clinically diagnosed atrial fibrillation (AF) would benefit from anticoagulation. However, less is known about the common entity of asymptomatic AF discovered on implantable devices. Two decades of data suggest that for individuals with asymptomatic AF episodes >24 hours, the risk for stroke and systemic embolization (SSE) approaches that of clinically diagnosed AF and thus, depending on CHA₂DS₂-VASc score, anticoagulation is warranted (SSE risk seems minimal when AF lasts <5 minutes). To examine whether asymptomatic AF durations between 5 minutes and 24 hours increase SSE risk and thus warrant anticoagulation, researchers linked a manufacturer's device database with electronic health records to examine the interaction of baseline CHA₂DS₂-VASc score, AF duration, and SSE rates in 21,768 non-anticoagulated patients with implanted devices. Several authors are employed by the device manufacturer.

SSE risk was lowest in patients with CHA_2DS_2 -VASc score of 0 or 1 regardless of device-detected AF duration. Those with a score of 2 would likely benefit from anticoagulation if AF lasted >24 hours. Patients with scores of 3 or 4 would likely benefit from anticoagulation if device-detected AF was >6 minutes. Those with scores \geq 5 may benefit from anticoagulation regardless of AF.

COMMENT: This analysis strengthens previous observations that device-detected AF \geq 24 hours is as thrombogenic as clinically detected AF. Clinicians may find the interaction between AF duration and CHA₂DS₂-VASc score useful when assessing SSE risks and deciding about anticoagulation. The study provides new data for device-detected AF between 5 minutes and 24 hours: If the CHA₂DS₂-VASc score is \geq 3, then anticoagulation may be beneficial. This clinically relevant observation will affect how I counsel patients about treatments. However, I do not think the evidence supports anticoagulation for those with scores \geq 5 but without AF. Ongoing randomized, controlled studies seek to answer this question.

JAMA Neurol 2019 Oct 14

Feasibility and Outcomes of Thrombectomy for Pediatric Stroke

Endovascular therapy is feasible but remains off-label for acute ischemic strokes in children.

The major trials that demonstrated the value of endovascular thrombectomy (EVT) for patients with acute ischemic stroke were all conducted in adults. Although much less common, potentially disabling strokes can also occur in children. These strokes have various mechanisms, including cardioembolism, arteriopathies, and cryptogenic events. Because data are sparse on outcomes of EVT in children with stroke, researchers conducted a review of children <18 years who were treated with EVT for acute ischemic stroke at 27 centers. The study included 73 patients (median age, 11.3 years; 51% male). The primary outcome was change in the pediatric NIH Stroke Scale (PedNIHSS) score from admission to day 7. Secondary outcomes included the modified Rankin Scale (mRS) score at 6 and 24 months.

Of the strokes recorded, 86% were in the anterior circulation and 82% were treated with stent retrievers, 44% were embolic, and the median time from onset to recanalization was 4 hours. The median PedNIHSS score decreased from 14 on admission to 4 by day 7. Long-term neurologic outcomes were good for most patients, with a median mRS of 1 at 6 and 24 months. The rate of serious complications was low (symptomatic intracerebral hemorrhage rate, 1.4%). One patient had postprocedural major bleeding and four patients had documented vasospasm.

COMMENT: This study provides evidence that in carefully selected children with acute ischemic stroke, EVT appears safe and is associated with good outcomes. Notably, this was not a randomized trial and only certain candidates were treated, as reflected in the number of patients enrolled per center. However, in hospitals with interventional expertise and in children with acute, potentially disabling strokes, EVT appears to be a reasonable (but off-label) treatment option.

Managing Pregnancy in Women with Myeloproliferative Neoplasms

Aspirin and interferon improved live birth rates among pregnant women with essential thrombocythemia or polycythemia vera.

Myeloproliferative neoplasms (MPNs) are typically diagnosed later in adulthood, but some patients with essential thrombocythemia (ET) and polycythemia vera (PV) present before the age of 40. For younger women with MPNs, pregnancies are high risk, and multidisciplinary collaboration is required, yet hematologists have scarce data to support recommendations.

Now, investigators have conducted a meta-analysis of 22 studies involving 1210 pregnancies among 767 women with MPNs to determine whether treatments with low-molecular-weight heparin (LMWH), aspirin, and interferon improved outcomes. Of these studies, 15 included women with ET, 3 included women with PV, and 4 included women with any classical MPN; 19 studies were retrospective.

Key findings included the following:

- The live birth rate was 71.3% overall and was 71.1% for women with ET and 66.7% for women with PV; 59.1% of miscarriages occurred in the first trimester.
- Odds of a live birth were improved with the use of aspirin compared with observation (odds ratio, 8.6) but not by adding LMWH to aspirin or using LMWH alone.
- Odds of a live birth were improved with the use of interferon with or without aspirin or heparin compared with observation (OR, 9.7).
- Preeclampsia occurred in 3.1% of pregnancies; the pooled incidences of venous thrombosis, arterial thrombosis, and postpartum hemorrhage were 1.5%, 1.3%, and 1.5%, respectively.
- JAK2 mutational status did not affect the live birth rate.

COMMENT: These results demonstrate that the use of aspirin and interferon might improve live birth rates for pregnant women with ET or PV. However, such interventions did not affect maternal outcomes. Although based on moderate quality of evidence, these findings will help guide hematologists in this setting. The challenge is to identify which women with otherwise low-risk ET or PV will benefit most. As the authors note, prospective international collaborations will be required to add to the evidence base.

CITATION(S): Maze D et al. Association of treatments for myeloproliferative neoplasms during pregnancy with birth rates and maternal outcomes: A systematic review and meta-analysis. *JAMA Netw Open* 2019 Oct 2; 2:e1912666. (https://doi.org/10.1001/jamanetworkopen.2019.12666)

Br J Psychiatry 2019 Sep 30

CBT Is Ineffective for Depression in Individuals with Advanced Cancer

The delivery of usual care by clinicians in multiple disciplines with cancer expertise worked just as well as cognitivebehavioral therapy.

Depression is unfortunately common in individuals with advanced cancer. Cancer patients are prone to medication side effects and drug interactions and face unique challenges that might be more easily met with psychotherapy, such as

cognitive-behavioral therapy (CBT), than with medications. Although CBT is the most validated psychological treatment for depression, it has not been well studied in patients with advanced cancer. In a U.K. randomized, controlled trial, investigators compared the efficacy of CBT (12 sessions over 3 months) plus treatment as usual (TAU) or TAU alone in 230 patients having a broad range of cancers.

CBT patients received a mean of 4.7 sessions (36% received no CBT sessions); the quality of delivered CBT was rated as highly proficient. TAU included multiple providers (oncologists, nurses, palliative care clinicians) and seemed akin to integrated or collaborative care. In analyses adjusting for antidepressant use, educational level, and therapist clustering, the two treatments did not differ at 6, 12, and 24 weeks, each treatment producing a minimal improvement (range, 6%–22%) in depression symptoms. Estimated change per CBT session was so small that even attendance at all 12 sessions would not have produced a substantive effect.

COMMENT: This disappointing result runs counter to the demonstrated efficacy of CBT in depressed individuals with other medical conditions. The finding might reflect the medical severity of advanced cancer, which can involve symptoms indistinguishable from depression (fatigue, amotivation, insomnia) that could both constrain participation and be unresponsive to CBT. Alternatively, the collaborative-care approach might have maximized the possible improvement in this population. Personalizing treatment to fit individuals and the unique aspects of their illnesses (as might occur with multidisciplinary integrated care) might be especially effective for depression in the context of serious medical illness.

J Am Acad Child Adolesc Psychiatry 2019 Aug 29

Interventions for Growth Suppression in Medicated Youth with ADHD

Neither drug holidays nor caloric supplementation appears to reverse medication-induced changes in height trajectory.

To formally assess the efficacy and feasibility of drug holiday and weight-recovery treatments (WRTs) on growth in children receiving stimulant medication (MED), investigators randomly assigned 230 children with attention-deficit/hyperactivity disorder (ADHD; age range, 5–12 years; 95% treatment-naive) to MED or behavior therapy (BT) in a 4:1 ratio. Participants with sustained declines in body-mass index after 6 months (71 children; 43% of medication users) continued MED (or, in the case of BT recipients, began MED) and were randomized to one of three WRTs: caloric supplementation (CS; a daily 150-kcal drink); drug holiday (DH; treatment limited to school days plus switch to drug formulations with shorter duration); or monthly monitoring (MON) of height and weight. The primary analysis was based on 10 months of intervention.

Compared with unmedicated controls, those receiving MED treatment showed significant reductions in standardized weight and height velocities. Adherence to CS and DH conditions was good, producing statistically significant increases in daily caloric intake and decreases in weekly medication exposure, respectively. Participants in all three groups gained significantly more weight at 10 months than their prerandomization trajectories had implied. The MON group gained an additional 1.8 kg, the DH group, 3.4 kg, and the CS group, 3.0 kg. However, no increase in height velocity was observed after randomization to any treatment group.

COMMENT: Despite the relatively small study size and relatively short window for the primary analysis, these data highlight the risks for growth suppression associated with prolonged exposure to central nervous system stimulants in youth and the need to explore potential mitigation strategies.

CITATION(S): Waxmonsky JG et al. A randomized controlled trial of interventions for growth suppression in children with attention-deficit/hyperactivity disorder treated with central nervous system stimulants. *J Am Acad Child Adolesc Psychiatry* 2019 Aug 29; [e-pub]. (https://doi.org/10.1016/j.jaac.2019.08.472)

JAMA Netw Open 2019 Oct 2; 2:e1912463

ADHD and Teenage Pregnancy Rates

In a Swedish nationwide study, having attention-deficit/hyperactivity disorder was associated with a fivefold greater risk for teenage pregnancy.

Although attention-deficit/hyperactivity disorder (ADHD) is associated with externalizing and risk-taking behaviors, including early sexual activity, the extent of teenage pregnancies in girls and women with ADHD has been little explored. To learn more, these investigators examined data from 2001 through 2014 in Swedish national registries (covering 98% of births).

The study cohort involved 6410 women and girls with ADHD (mean age, 25) and 377,693 without ADHD (mean age, 28). Teenage deliveries (before age 20) occurred in 15% of the ADHD group compared with 3% of the non-ADHD group, a significant difference. Teenage mothers with ADHD had higher rates of obstetrical and perinatal complications, underweight, obesity, and smoking (first-trimester smoking, 26% vs. 6%; continuing into the third trimester, 20% vs. 4%). Alcohol or drug use disorder was found in 15% of the ADHD group (odds ratio, 20). Comorbidities in the ADHD group were substantial for bipolar disorder (OR, 18), psychotic conditions (OR, 8), and emotionally unstable personality disorder (OR, 22). During pregnancy, 8% of the ADHD group used ADHD medications (stimulant or nonstimulant), and 16% used antidepressants.

COMMENT: The overall rate of teenage pregnancies in Sweden (3%) is considerably lower than U.S. rates (in various populations, 6%–15%), but in this study, the rate among those with ADHD is notably high. The researchers do not differentiate risks for pregnancy by ADHD subtype, adequacy of ADHD treatment, and use of health or mental health counseling services. Given the substantial obstetrical, psychiatric, and social risks associated with teenage pregnancies, general and mental healthcare clinicians should proactively offer sex and contraceptive education and services to these patients.

CITATION(S): Skoglund C et al. Association of attention-deficit/hyperactivity disorder with teenage birth among women and girls in Sweden. *JAMA Netw Open* 2019 Oct 2; 2:e1912463. (https://doi.org/10.1001/jamanetworkopen.2019.12463)

DNA Testing to Confirm Diagnosis of Pancreatic Lesions

KRAS mutations were identified in malignant, but not benign, solid pancreatic lesions.

Endoscopic ultrasound-guided fine-needle aspiration (EUS FNA) is the most common and successful technique used in evaluating solid pancreatic lesions for possible malignancy. But up to 10% to 15% of lesions sampled by EUS FNA may yield indeterminate pathology results.

Now, investigators in Denmark have conducted a single-center, retrospective study of patients with solid pancreatic lesions to determine if DNA testing would improve diagnostic accuracy in patients with inconclusive EUS FNA results without requiring them to undergo traditional follow-up procedures such as repeat EUS FNA, CT-guided biopsy, or, rarely, surgical biopsy.

DNA analysis of genes commonly mutated in cancer was performed on cytology specimens from 39 patients: 16 had suspected malignancy on EUS that was confirmed by cytologic analysis to be malignant (malignant group), 13 had suspected malignancy on EUS but had cytologic results that were benign (inconclusive group), and 10 had EUS and cytologic results that were consistent with benign disease (benign group). Patients were followed with regards to other testing and clinical outcome to reach a final diagnosis.

The incidence of *KRAS* mutations was significantly more common in the malignant and inconclusive groups, and all patients in the inconclusive group were ultimately diagnosed with malignancy. No patients with a benign final diagnosis had a *KRAS* mutation.

COMMENT: This study demonstrates that currently available genetic tests can be used to analyze tissue samples from patients with solid pancreatic lesions to help identify those patients who harbor a malignancy. Although the study is small and retrospective, the results are striking. Larger prospective studies on this topic are likely forthcoming, and, if similar results are shown, genetic testing could become a standard part of the diagnostic algorithm for these patients.

CITATION(S): Plougmann JI et al. DNA sequencing of cytopathologically inconclusive EUS-FNA from solid pancreatic lesions suspicious for malignancy confirms EUS diagnosis. *Endosc Ultrasound* 2019 Sep 25; [e-pub]. (https://doi.org/10.4103/eus.eus_36_19)