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Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

SPECIAL FEATURE

'It's the Worst Headache of My Life:' Subarachnoid Hemorrhage — A Brief Review

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

INTRODUCTION AND EPIDEMIOLOGY

Subarachnoid hemorrhage (SAH) is a stroke syndrome, defined as "rapidly developing neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the subarachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma."[1] It is a dire condition with high morbidity and mortality.

SAH accounts for about 5-10% of all strokes, affecting 8-10 per 100,000 population or about 30,000 persons in the United States yearly. Patients with SAH are usually between ages 40 and 60 years (mean 55 years); women and African Americans are at increased risk. Sixteen percent of these patients die at the time of the initial bleed. The overall mortality rate is high at 30-45%; two-thirds of survivors are left with significant permanent neurological impairment.[2,3]

ETIOLOGY

SAH occurs most commonly (85% of the time) as a result of rupture of a congenital central nervous system (CNS) aneurysm. This article will focus on that. Other causes include arteriovenous malformations, vasculitis, amyloid angiopathy, etc. The rate of incidentally noted CNS aneurysm (from radiographic or autopsy studies) is high at 5% in the United States (closer to 10% in patients with a strong family history of CNS aneurysms) but, as noted above, only a small number of these will rupture. About 30% of affected patients have multiple CNS aneurysms. The overall estimated risk of rupture is ≤ 1% yearly, with considerably increased risk for aneurysms > 10 mm. The majority of CNS aneurysms are of the saccular (or berry) type and involve the large arteries

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rising from the Circle of Willis, particularly the anterior and posterior communicating arteries.[2,4,5]

Certain genetic conditions and connective tissue disorders, such as polycystic kidney disease and Ehler-Danlos syndrome, are associated with an increased likelihood of CNS aneurysm formation and SAH. Even in the absence of known genetic conditions, a family history of SAH increases an individual's risk. Other significant risk factors for SAH include hypertension, alcohol, or cocaine abuse.[4,6] Current cigarette smoking is the most significant and well-documented modifiable risk factor. It has a dose-dependent effect that disappears within a few years of smoking cessation.

CLINICAL PRESENTATION

CNS aneurysms are generally asymptomatic until rupture occurs. The acute symptoms of SAH are primarily a reflection of increased intracranial pressure due to the release and spread of blood in the subarachnoid space and cerebrospinal fluid (CSF).

More than 80% of patients will present with headache and it is important to maintain a high index of suspicion for possible SAH. (SAH accounts for only about 1% of headaches presenting to the emergency department; the diagnosis may be missed initially in 5-25% of patients.) The classic history is that of abrupt onset of severe headache, typically "the worst headache of my life" with "thunderclap" quality; that is, reaching its most severe and intense pain within seconds to a few minutes of onset. This latter feature is most specific for SAH. The headache may come on during exertion or rest or may even awaken the patient from sleep. In up to 40% of patients, this "worst headache" may be preceded by a sentinel headache (a smaller leak from the aneurysm) 2-8 weeks prior. About one-third of patients present with headache as the only complaint, but in others, associated symptoms occur including nausea, vomiting, photophobia, neck pain or stiffness, seizure, or altered level of consciousness. It is uncommon to find focal neurological deficits on initial presentation.[7,8]

Hypertension and tachycardia are often present. Electrocardiographic abnormalities (thought to be of neurogenic etiology) are common, including QTc prolongation or ST and T changes mimicking primary cardiac ischemia. Malignant ventricular arrhythmias may occur; sudden cardiac arrest is the presenting finding in up to 3% of cases of SAH.[9]

DIAGNOSIS

The initial diagnostic study of choice is a noncontrast head CT; the sensitivity of this for SAH is close to 100% for the first few hours to 3 days after the bleed. Accuracy of noncontrast head CT for SAH declines over time because of the normal circulation of the CSF and breakdown of blood. If the head CT is negative and clinical suspicion for recent SAH is high, lumbar puncture should be performed next to look for xanthochromia, which is the yellowish discoloration of CSF due to the presence of bilirubin. It may take 6-12 hours after the initial bleed for degradation of blood and development of xanthochromia.

Once SAH is confirmed, it is essential to image the intracranial vessels as quickly as possible to look for and treat the underlying source of the bleed before rebleeding occurs. Head CT angiogram (CTA) will usually identify the source (the aneurysm), but small aneurysms (< 3 mm) may be missed. For patients with SAH and negative CTA, digital subtraction cerebral angiography must be considered.[8,10,11]

Multimodal (including MRA) brain MRI has similar sensitivity to CT/CTA and may eliminate the need for contrast medium. However, acquisition of images takes longer, availability/experience may be limited, and cost is generally greater than for CT; thus this is not recommended as the first-line diagnostic study for most patients.[7]

In 15-22% of patients, no clear cause of SAH is found on the initial studies,

and repeat angiogram is recommended in 4-14 days.[12]

TREATMENT

SAH is a clinical emergency due to its high morbidity and mortality, which are further worsened by any delays in definitive treatment of the underlying aneurysm. The priority is to quickly occlude the ruptured aneurysm to prevent rebleeding and then avoid vasospasm. Usual ICU supportive care and monitoring for other problems (seizures, hydrocephalus, elevated intracranial pressure [ICP]) is also essential.

All patients with SAH should be admitted to and monitored in an ICU with involvement of neurosurgical and critical care providers and hourly assessment of vital signs and neurological examination. Cautious blood pressure (BP) control is important to minimize risk of rebleeding, with goal SBP ≤ 160-180 mmHg, at least until definitive treatment of the aneurysm. Nicardipine is recommended as first-line therapy. Measures should be taken to avoid raising ICP: quiet bed rest, analgesics, antipyretics, (central fever occurs in about 20% of patients), antiemetics, etc.[10,12] Careful monitoring of the airway and usual measures to avoid aspiration are essential. Provide deep venous thrombosis prophylaxis with pneumatic compression stockings. Once the aneurysm is obliterated, pharmacologic prophylaxis may be added. Usual glucose control is indicated. Seizure prophylaxis is not universally recommended, although some experts suggest considering it (usually with levetiracetam), but treatment should be initiated right away if seizure occurs. Finally, for patients on warfarin, anticoagulation should be reversed and antiplatelet agents should also be held.[8]

The risk of rebleeding in the first 72 hours after SAH is quite high, particularly within the first 6-24 hours. Occlusion of the ruptured aneurysm is the only effective preventive measure/treatment and should be performed as soon as possible in the 72-hour window. There are two possible approaches, endovascular coiling or neurosurgical clipping. In general, when an aneurysm is amenable to either approach, coiling is recommended. There has been one large, multicenter, randomized, clinical trial of > 2000 patients that provides support for this, demonstrating reduced death and disability (24% vs 31%) at 1 year in those treated with coiling.[13] However, it may be more difficult to achieve complete obliteration of the aneurysm with coiling and recurrence of aneurysm and bleeding may occur; thus, delayed follow-up imaging is essential, with retreatment if there is evidence of persistence or recurrence of aneurysm.[13] For certain clinical scenarios (such as advanced patient age, poor neurological status at presentation, wide-mouthed aneurysm, and middle cerebral artery aneurysm), surgical clipping is recommended as the first-line intervention.[10,12]

Symptomatic vasospasm occurs in up to 30% of patients after SAH, leading to cerebral ischemia and infarction, and this is the leading cause of morbidity and mortality in SAH. It is believed to be caused by imbalance in vasoactive mediators due to the impact of metabolites of blood cells in the CNS. Vasospasm typically begins on or after day 3, peaks at about day 7-10, and may take up to 3-4 weeks to fully resolve. Patients develop new focal neurological findings or altered level of consciousness (persistent decline in Glasgow coma score by at least 2). Transcranial Doppler ultrasound will confirm the diagnosis. Nimodipine (60 mg orally every 4 hours for 21 days) is currently the only proven effective therapy and is standard of care for prevention of vasospasm. It has been shown to significantly reduce the risk of secondary ischemia, poor neurological outcome, and death, although primary vasodilation may not be the mechanism of action.[14] If symptomatic vasospasm occurs, supportive treatment with "triple H" therapy should be initiated: i.e., hypertension (induced, with vasopressors), hypervolemia (current practice suggests aiming for euvolemia), and hemodilution (mild to moderate, with maintenance fluids), with the goal of increasing mean arterial pressure and, thus, cerebral perfusion pressure. Endovascular treatment (intra-arterial infusion of vasodilators or balloon angioplasty) for symptomatic vasospasm is a newer approach that shows promise in some case series and clinical reports. It appears to be most effective when used early, within 1-2 hours of onset of symptoms, and produces good

radiographic results (resolution of vasospasm on imaging). However, the duration of effect is variable, there are significant potential risks (vessel injury, rebleeding), and the extent and significance of short- and long-term clinical improvement are unknown thus far.[10,12,15]

Delayed cerebral ischemia can develop in patients with SAH, even in the absence of vasospasm. It remains unclear how to prevent or detect this early on and investigations are ongoing. At this time, there are no data to support routine intracerebral monitoring such as ICP monitoring with ventricular or lumbar drains, continuous electroencephalography, or jugular bulb oximetry.

Hydrocephalus is commonly seen radiographically, but patients may be asymptomatic and findings may resolve spontaneously in about half of affected patients within 24 hours. When persistent, treatment is generally with placement of an extra-ventricular drain (less commonly, a lumbar drain).[10]

There are ongoing investigations of medical therapies for SAH. For prevention of rebleeding, antifibrinolytics (such as tranexamic acid) continue to be discussed; older studies showed reduced risk of rebleeding, no impact on other outcomes, and increased risk of cerebral ischemia or systemic thromboemboli, but shorter-term use may have greater benefit without the adverse effects and thus has been advocated by newer reports.[16] Recombinant factor VIIa has been tried for similar reasons but has been associated with systemic venous thromboemboli. For prevention of vasospasm, magnesium, statins, tirilazad, and endothelin-receptor antagonists have all been tried, thus far with equivocal or negative results.[17,18]

PROGNOSIS

The best predictors of outcome are the patient's neurological condition on presentation, age (inverse relationship), and the amount of extravasated blood seen on CT scan. There are several standardized scoring systems used to define SAH for documentation and clinical communication. The Hunt and Hess scale rates neurological status from grade 1 (asymptomatic or mild headache) to grade 5 (coma and posturing); the World Federation of Neurological Surgeons' score incorporates the Glasgow Coma Scale score and the presence of motor deficits. Two other commonly used scoring systems, Fisher scale and Classen grading system, describe the extent of blood on head CT. Unfortunately, none of these scoring systems are well validated. They have not been prospectively compared to each other and have variable accuracy and utility for predicting outcomes.[19]

CONCLUSION

Accurate diagnosis and timely treatment of aneurysmal SAH require a high index of suspicion, rapid imaging (noncontrast head CT, possible lumbar puncture, and some sort of angiographic study), definitive occlusion of the aneurysm to prevent rebleeding, and aggressive supportive care to prevent or limit delayed cerebral ischemia. Even with the best care, aneurysmal SAH carries very high morbidity and mortality. Our understanding of SAH and how best to manage it remains in its infancy, and ongoing investigation is essential to improve future outcomes. ■

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ABSTRACT & COMMENTARY

Preventing ICU Infections: An Effective Application of An Old Public Health Strategy

By Michael Young, MD

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

SYNOPSIS: **Despite better compliance with hand hygiene and screening, use of isolation, and other techniques, ICUs remain notorious breeding grounds for hospital-acquired infections. A universal decolonization strategy reduces the total number of ICU bloodborne infections.**

SOURCE: Huang SS, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;368:2255-2265.

INTRODUCTION

In the 1840s, the Hungarian physician Ignaz Semmelweis demonstrated that maternal mortality was reduced by 90% when physicians washed their hands with a chlorinated solution prior to doing pelvic exams on women in labor. The physician community at that time was harshly skeptical of Semmelweis's observations and recommendations. Women of the time were aware that something was lethal about having babies in the hospital. Some women in the 1840s preferred having their babies literally in the street vs the high-mortality obstetrical wards in teaching hospitals. A century and a half later, hand hygiene is widely accepted as a technique to reduce transmission of infections among hospitalized patients. Uniform compliance with recommended hygiene practices remains disappointing.

About 100 years after Semmelweis's discovery that hand hygiene really matters, ICUs came into existence. It made sense to clinicians to cluster the sickest patients in one area of the hospital to more conveniently apply new technologies such as mechanical ventilation, central venous lines, and the rapidly evolving skill sets of clinicians who focused on managing critically ill patients. Unfortunately, those life-preserving technologies and the ICU population of patients and their clinicians became reservoirs of methicillin-resistant *Staphylococcus aureus* (MRSA) as early as the 1960s. By 2005, it was estimated that hospitals see more than 18,000 deaths/year from MRSA — more deaths than those reported from AIDS and breast cancer combined. The ICU was no small contributor to the rising death toll from MRSA infections.

In the past two decades, a number of strategies have come into use to prevent the spread of MRSA and other infectious agents in the ICU. The effectiveness of some of these strategies, such as screening patients for MRSA, isolation, contact precautions, and decolonization, has been uncertain. The study by Huang and colleagues provides clinicians, nurses, and infection control specialists much needed guidance.

ABSTRACT

The authors conducted the study in 43 Hospital Corporation of America hospitals, including 74 ICUs. A 12-month baseline period was followed by an 18-month intervention period in which participating hospitals were randomized, using a stratified technique, to one of three infection control groups. In group 1, > 90% of ICU patients received screening and isolation if their nasal swab was positive for MRSA. Contact precautions were used among patients who screened positive for MRSA. In group 2 ("targeted decolonization"), MRSA screening and isolation occurred as in group 1. MRSA-positive patients underwent a 5-day decolonization process. In group 3 ("universal decolonization"), patients were not screened on admission to the ICU. All ICU patients in group 3 received twice-daily intranasal mupirocin for 4 days, plus daily baths with chlorhexidine-soaked cloths during the patients' entire ICU stay.

Adherence to the infection control interventions in each of the three groups was encouraged by monthly educational teleconferences and use of on-site hospital personnel. Infections/pathogens

Table. Adjusted Hazard Ratios for Major Outcomes			
	MRSA clinical culture positive	MRSA bacteremia	All bloodborne infections
Intervention Group 1 (Screening and Isolation)	0.92	1.23	0.98
Intervention Group 2 (Targeted Decolonization)	0.74	1.19	0.77
Intervention Group 3 (Universal Decolonization)	0.64	0.74	0.55
P value	0.01	0.18	< 0.001

were defined using Centers for Disease Control and Prevention (CDC) criteria. Compliance rates of 85% were cited.

There were nearly 100,000 patients enrolled in each of the three groups and the groups had largely similar baseline demographic characteristics. MRSA-positive isolates and the risk of developing a bloodborne pathogen were significantly reduced by universal decolonization. With universal decolonization, the number needed to treat to prevent one bloodstream infection was 54 ICU patients. The rate of blood-borne infections from MRSA was not reduced by either targeted or universal precautions (*see Table.*)

■ COMMENTARY

Limitations of the study include lack of an explicit and detailed protocol for each of the three groups. In addition, it remains uncertain if routine use of chlorhexidine and mupirocin will lead to resistance. Severity of illness on ICU admission was not reported. Most of the hospitals included in the study were community hospitals, so it remains unknown if similar results will be seen in large teaching hospitals. It is also unclear why a decrease in MRSA colonization rates, the primary outcome, was not associated with a decrease in MRSA bacteremia.

Study strengths are considerable. Implementing universal decolonization was undertaken with existing personnel without apparent increased costs. The sample size was substantial. Randomization ensured similar baseline characteristics. The size of the reduction in MRSA colonization and positive blood cultures was both statistically and clinically significant. Finally, use of universal decolonization techniques in ICUs is becoming a more common practice.

Should this study change standard infection control measures in our ICUs? I believe that the answer to this question is an emphatic yes. As this study demonstrates, isolation and contact precautions lack effectiveness at preventing infection, and they also reduce clinician bedside presence. Arguably, it is intensivist bedside presence that is at least partly responsible for the improved patient outcomes seen with the intensivist "high intensity" model. In addition, from the use of "bundles" in the ICU over the past 10 years, such as those used for ventilator-associated pneumonia, central line infection reduction, and early resuscitation for sepsis, we have learned that ICU outcomes dramatically improve when a practice becomes universal and applied to all rather than applied selectively or simply at physician discretion.

Will many or all ICUs make the change to universal decolonization soon? This seems less certain, but my forecast is largely positive for the following reasons. We recognize that changes in hospital infection control practices involve complicated organizational and cultural shifts. However, physicians and hospitals change practice patterns over a period of months rather than over years if certain forces align, including: a convincing level of medical evidence; minimal cost to implementing the intervention; the intervention makes "life" easier for the clinicians; and authoritative groups such as the Society of Critical Care Medicine, the American Thoracic Society, and the CDC endorse the change in practice. Finally, the "stick" used by regulatory bodies such as the Centers for Medicare & Medicaid Services can provide powerful incentives to accelerate change in practice.

In summary, this is the time for us to develop a new infection control bundle in the ICU that includes universal decolonization. If Semmelweis were alive today, he would surely agree with this approach. On the other hand, he might be distraught to learn that in 2013 we are still struggling to achieve better compliance with hand hygiene. ■

ABSTRACT & COMMENTARY

Continuous EEG During Therapeutic Hypothermia After Cardiac Arrest — Is it Useful?

By Eric C. Walter, MD, MSc

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

SYNOPSIS: Moderate or severe EEG abnormalities are frequently seen in patients during therapeutic hypothermia following cardiac arrest and these findings are associated with poor outcomes.

SOURCE: Crepeau AZ, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest. *Neurology* 2013;80:339-344.

Electroencephalograms (EEGs) have been recommended to monitor for seizure activity in patients undergoing therapeutic hypothermia following cardiac arrest.[1] Data supporting this recommendation are limited. In 2009, the Mayo Clinic instituted continuous EEG (cEEG) monitoring among all patients undergoing therapeutic hypothermia following out-of-hospital cardiac arrest (ventricular fibrilation, witnessed asystolic arrest, or pulseless electrical activity). In this article, Crepeau and colleagues retrospectively reviewed EEG data from 54 consecutive patients to determine the prognostic significance of EEG abnormalities and develop an EEG grading system. They then sought to validate this grading system by correlating it with neurologic outcomes. EEG findings were graded as mild, moderate, or severe. Neurologic outcomes were graded according to the Cerebral Performance Category. Outcomes were dichotomized as good (normal or slight disability or moderate disability but awake and alert) or poor (conscious patients with a severe disability, or persistent vegetative state, or dead/brain dead).

During hypothermia, 67% of patients had moderate (56%) or severe (11%) EEG findings. Similar results were seen during rewarming and normothermia. Seizures occurred in four patients during hypothermia and one patient during rewarming (total of 9%). All seizures were generalized and occurred in patients with a severe EEG background prior to the seizure. Good neurologic outcomes were seen in a surprisingly high 33 (61%) patients. Of the 21 patients with a poor outcome, 19 died. Having a severe EEG finding was strongly associated with a poor outcome. A severe EEG was seen in 16 of 21 (76%) patients with a poor outcome. Despite treatment, no patients with seizures had a good outcome. Six patients had only mild EEG findings and all had a good neurologic outcome.

COMMENTARY

Prognostication after out-of-hospital cardiac arrest has challenged and frustrated critical care physicians for decades. Recently, therapeutic hypothermia has been shown to improve neurologic outcomes, and our previous strategies for estimating neurologic prognosis may no longer be adequate in this era. To this end, Crepeau and colleagues provide this retrospective report. While the study was retrospective, they enrolled nearly all patients who underwent therapeutic hypothermia with cEEG monitoring. They developed a relatively simple EEG grading system and this system had reasonably good correlation with prognosis. That should not be overly surprising. One might expect that those patients with more severe brain injury would be more likely to have a severe EEG and would be more likely to have a poor prognosis. Indeed, 76% of patients with a severe EEG had a poor outcome. While this is helpful it is by no means definitive, as the remaining 24% of patients with a severe EEG had a good outcome. The number of patients with a mild EEG was small (six), but notably all had a good outcome.

The major limitation of this study was that the treatment team was aware of EEG findings. It is probable that this information influenced both clinicians and families — a severe EEG leads to estimation of a poor prognosis, which leads to potential limitation of care, thus creating a self-fulfilling prophecy.

Is cEEG useful during therapeutic hypothermia following cardiac arrest? The jury is still out. The goals of cEEG are to detect potentially treatable conditions such as seizures and to improve prognostication. This study adds to previous studies showing that seizures and malignant EEG patterns are associated with poor neurologic outcomes.[2,3] However, seizures may just be a

marker of a severely injured brain. Treatment of seizures in this study and others[2,3] has not been shown to improve neurologic outcomes. It is also too early to advocate for cEEG as a prognostic tool. The "self-fulfilling prophecy" is a serious limitation in observation studies such as this one. In addition, cEEG is extremely labor intensive and expensive. We do not know how it compares to other tools used currently to estimate prognosis. Perhaps the old fashioned bedside exam may still be useful. ■

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CME/CNE Questions

1. Subarachnoid hemorrhage:

a. is the most common cause of stroke.
b. occurs most commonly in persons older than 60 years of age.
c. has a low mortality rate at 5-10%.
d. leaves the majority of patients with significant neurological deficits.
e. is only rarely caused by aneurysms.

2. Patients with subarachnoid hemorrhage most commonly present with:

a. visual disturbance.
b. headache.
c. hemiplegia.
d. hypotension.
e. seizure.

3. Which of the following infection control techniques is best at reducing the risk of bloodborne infections in the ICU?

a. Targeted decolonization
b. Universal decolonization
c. Screening and isolation
d. Treatment of all colonized patients with systemic antibiotics
e. None of the above

4. Compared to targeted decolonization and screening/isolation techniques, the number needed to treat to prevent one bloodstream infection in ICU patients with the use of universal decolonization was shown to be which of the following?

a. 8
b. 20
c. 54
d. 136
e. 542

5. In the Mayo Clinic study, a severe EEG finding during therapeutic hypothermia following cardiac arrest was associated with which of the following?

a. A good neurologic outcome
b. The development of severe hypotension
c. A poor neurologic outcome
d. Abnormal somatosensory evoked potentials
e. Sudden cardiac death

6. With respect to seizures during therapeutic hypothermia following cardiac arrest:

a. they are most often due to infection.
b. treatment of seizures in this population has not been shown to improve neurologic outcome.
c. they should be treated with paralytic agents.
d. they are associated with a good neurologic outcome.
e. they were preceded by mild EEG findings in this study.

CME/CNE Objectives

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

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

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Food Allergy in IBS: Patch Testing

Source: Stierstorfer MB, et al. Food patch testing for irritable bowel syndrome. *J Am Acad Dermatol* 2013;68:377-384.

We have, as yet, no fully satisfactory etiologic explanation for the symptom complex recognized as irritable bowel syndrome (IBS). Yet, demonstration of various derangements — hypersensitivity to neurogenic stimuli, altered bowel flora, dysregulation of serotonin — has been seen in subgroups of persons with typical IBS. Results from IBS trials of non-systemic antibiotics (e.g., rifaximin) demonstrate improvements in IBS symptoms and support bacterial flora imbalance in some, but not all, IBS subjects.

IBS patients commonly report foods that exacerbate symptoms. Could these food sensitivities represent actual food allergy, and contribute etiologically to IBS? A variety of commonplace foods and food additives have been documented to cause allergic *cutaneous* contact dermatitis (type-4 hypersensitivity). Could similar responses lead to inflammatory changes in the gut and symptoms of IBS?

Stierstorfer et al performed patch testing in IBS subjects (n = 51) using up to 40 different foods or food additives that have been previously recognized as implicated in food hypersensitivity. Fifty-eight percent of subjects had one or more patch test results indicating possible food sensitivity, and when the "offending" food was eliminated from the diet, about two-thirds of subjects reported symptomatic improvement. Food allergy may play a more important role in IBS than previously recognized. ■

A Relationship Between Atrial Flutter and Sleep Apnea

Source: Bazan V, et al. Obstructive sleep apnea in patients with typical atrial flutter: Prevalence and impact on arrhythmia control outcome. *Chest* 2013;143:1277-1283.

Commonly recognized consequences of obstructive sleep apnea (OSA) include increased risk for hypertension, cardiovascular events, and arrhythmias, the most common of which is atrial fibrillation (AFib). Less well understood is the relationship between atrial flutter (AF) and OSA. Even though invasive treatment through catheter ablation is highly effective for AF, over the long term, as many as one-third of AF ablation patients develop postoperative AFib, which of course has its own toxicities.

Bazan et al evaluated a preoperative population of AF patients with polysomnography, none of whom had previously been diagnosed with or suspected of OSA. Overall, 82% of subjects were diagnosed with OSA, almost half of whom were graded as severe OSA.

Over the ensuing 12 months, use of continuous positive airway pressure (CPAP) in OSA patients who had received catheter ablation for AF resulted in a dramatic reduction in new postoperative AFib: from 46% (untreated) to 6% (treated).

OSA appears to be more commonplace in AF than previously recognized. Although a much larger randomized clinical trial will be necessary for confirmation, this small study suggests that for AF patients with OSA who are undergoing catheter ablation, CPAP substantially reduces the likelihood of postoperative AFib. ■

Beyond Hypertension: Metabolic Effects of Telmisartan

Source: Takagi H, et al. Telmisartan as a metabolic sartan: The first meta-analysis of randomized controlled trials in metabolic syndrome. *J Am Soc Hypertens* 2013;7:229-235.

It has not gone unnoticed that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can sometimes have a favorable effect on glucose metabolism in diabetics and prediabetics. Experts have opined that it is perhaps vascular dilation in the skeletal muscle compartment from renin-angiotensin-aldosterone system blockade that produces increased glucose utilization. One of the ARBs, telmisartan, in addition to its blood pressure-lowering effect, has been noted to have peroxisome proliferator-activated receptor (PPAR)-gamma activation activity, distinct from the other members of this drug class. PPAR-gamma activation could favorably impact metabolic syndrome, but individual clinical trials of telmisartan have been inconclusive in this regard.

Takagi et al performed a meta-analysis of clinical trials (n = 10) of telmisartan in patients (n = 546) with metabolic syndrome. Favorable effects were seen for

fasting glucose, insulin, and A1c. Of the 10 trials analyzed, only three included data on adiponectin, but results were also favorable for this metric.

Large clinical trials of telmisartan in patients with established vascular disease (e.g., TRANSCEND, n = 5926) have shown a nonsignificant trend toward less new onset diabetes, but the number of metabolic syndrome subjects in this trial was not specified.

Whether favorable changes seen in metabolic syndrome patients treated with telmisartan are sufficient to improve "hard" outcomes (myocardial infarction, cerebral vascular accident, diabetes mellitus) would require a very large clinical trial. ■

Risk of New Onset Diabetes with Statins

Source: Danaei G, et al. Statins and risk of diabetes: An analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care* 2013;36:1236-1240.

The oft-quoted "9% increase in new onset diabetes (NODM) due to statins" sounds pretty scary. What is left out of the aforementioned quote, however, is that the increased risk is a *relative*, not *absolute*, increase. To make the issue more concrete: In one of the largest meta-analyses (n = 91,000), we learned that statins increase risk for diabetes. Among 45,521 statin-treated patients, there were 2226 NODM cases (compared to 2052 of 45,619 placebo recipients); the incidence of NODM then was 4.89% in the statin group, compared to 4.5% in the placebo group, for an underwhelming risk increase of 0.39%. This would translate into a number needed to treat of 250 patients receiving a statin to induce one new case of diabetes. Not nearly so scary, huh?

The most recent analysis of NODM compiled data from the electronic medical records of 500 United Kingdom general practices (n = 285,864). Similar to the above mentioned meta-analysis, the absolute annual incidence in the United Kingdom dataset was 1.59% in statin users compared to 1.13% in nonusers.

Statins can cause NODM, but in trials of secondary prevention, risk of NODM is far outweighed by risk reduction for cardiovascular events. ■

Perimenstrual Asthma: A High-Risk Phenotype

Source: Rao CK, et al. Characteristics of perimenstrual asthma and its relation to asthma severity and control: Data from the severe asthma research program. *Chest* 2013;143:984-992.

Some women with asthma note a worsening of asthma related to onset of menses. In the National Heart, Lung, and Blood Institute Severe Asthma Research Program (SARP), 17% of women (92/483) reported that menses were a trigger for their asthma symptoms. Exploration of perimenstrual asthma (PMA) as a distinct phenotype has been prompted by the recognition of an association between PMA and asthma acuity. Indeed, near-fatal and fatal asthmatic events have been linked to PMA.

Evaluation of women identified with PMA from SARP found that nearly twice as many PMA subjects met criteria for classification as severe asthma than women without PMA. In addition, levels of asthma control were worse in PMA subjects, and they experienced greater urgent health care utilization. Aspirin sensitivity was found three times more often in PMA patients (30% vs 10%), as were nasal polyps (16% vs 5%).

At the current time, PMA is not a widely appreciated entity. In the United States, there are still approximately 5000 asthma deaths per year. Any phenotypic prototype that can help to identify an asthma population at greater risk of fatal or near-fatal asthma might be a step toward reducing the mortality burden of asthma. ■

What's the Durability of Lifestyle Change in Type 2 Diabetes?

Source: Jakicic JM, et al. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: The Look AHEAD trial. *Diabetes Care* 2013; 36:1297-1303.

Embarking on lifestyle change is widely reinforced early on by numerous incidental happenstances. First, response to diet is most prominent in the early weeks of dieting. Second, relative gains in fitness and strength are most obvious in the early weeks of dieting. Third, most support programs providing advisors for diet, exercise, and psychological aspects are "front-loaded" (greater frequency/intensity at first) to try and establish optimum patterns early on. Fourth, as one gains positive initial steps, observers and friends tend to be avid supportive "cheerleaders," a response that diminishes as the going gets tougher, occasional ground is lost, or ground gained is less visible.

Jakicic et al report on the outcome at 4 years in the Look AHEAD Research Group trial. Overweight or obese type 2 diabetics (n = 3942) were randomized to intensive lifestyle intervention (ILI) or standard care. ILI included weekly instructional/support sessions × 24, continuing with lesser (but still frequent) support on diet and exercise throughout 4 years time. Goal exercise time was 175 minutes a week of brisk walking or the equivalent. As perhaps is intuitive, the intervention group achieved and maintained better fitness levels, better A1c, and better weight control. Structured ILI programs can provide sustained benefits in overweight and obese type 2 diabetics. ■

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Is Naproxen the Safest NSAID for the Heart?

In this issue: NSAIDs and cardiovascular risk; new antithrombotic guidelines; warfarin during surgery; Pfizer selling Viagra online; azithromycin and cardiovascular risk; and FDA actions.

NSAIDs associated with less vascular risk

Naproxen may be the safest anti-inflammatory — at least when it comes to cardiovascular risk — according to a new study. Researchers from the United Kingdom undertook a meta-analysis of 280 trials of non-steroidal anti-inflammatory drugs (NSAIDs) vs placebo and 474 trials of one NSAID vs another. Main outcomes were major vascular events, major coronary events, stroke, mortality, heart failure, and upper gastrointestinal (GI) complications including bleeding. All NSAIDs and COX-2 inhibitors (coxibs) increased major vascular events except for naproxen (rate ratio [RR], coxibs 1.37 [95% confidence interval (CI), 1.14-1.66; $P = 0.0009$] and diclofenac 1.41 [95% CI, 1.12-1.78; $P = 0.0036$] mostly due to an increase in major coronary events). Ibuprofen also significantly increased the risk of major coronary events (RR 2.22, 95% CI, 1.10-4.48; $P = 0.0253$), but not major vascular events. Naproxen did not significantly increase the risk of major vascular events. Coxibs and diclofenac also significantly increased risk of vascular death, and there was a nonsignificant increase with ibuprofen, while there was no increase with naproxen. Heart failure risk was roughly doubled by all NSAIDs. The risk of upper GI complications was lowest with coxibs and highest with naproxen (coxibs 1.81, 95% CI, 1.17-2.81; $P = 0.0070$; diclofenac 1.89, 95% CI, 1.16-3.09; $P = 0.0106$; ibuprofen 3.97, 95% CI, 2.22-7.10; $P < 0.0001$, and naproxen 4.22, 95% CI, 2.71-6.56; $P < 0.0001$). The authors conclude that the vascular risks of diclofenac and possibly ibuprofen are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk (but higher GI risk) than other NSAIDs (*Lancet* published online May 30, 2013). The authors speculate that high-dose naproxen has fewer cardiovascular effects because it is the strongest inhibitor of COX-1, resulting in near complete suppression of platelet thromboxane biosynthesis (thus blocking platelet aggregation) throughout the 12-hour dosing interval. ■

New antithrombotic guidelines

A new guideline from the American Academy of Neurology gives primary care doctors guidance on periprocedural management of antithrombotic medications in patients with a history of stroke. Among the recommendations is that stroke patients undergoing dental procedures should routinely continue aspirin. Aspirin should also be considered for continuation in stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery. Aspirin should possibly be continued during other procedures such as virtroretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy/sphincterotomy, and abdominal ultrasound-guided biopsies. For stroke patients on warfarin, the guideline recommends continuation of the drug

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during dental procedures and probably during most dermatologic procedures. Other more invasive procedures should warrant discussion. The guideline states there is insufficient evidence to support or refute periprocedural heparin-bridging therapy to reduce thromboembolic events in chronically anticoagulated patients. Bridging therapy is probably associated with increased bleeding risk as compared with warfarin cessation, but the risk difference compared with continuing warfarin is unknown (*Neurology* 2013;22:2065-2069). ■

Continuing warfarin for surgery

In related news, a new study suggests that continuing warfarin for pacemaker or defibrillator surgery is safer than heparin bridging. Nearly 700 patients with an annual risk of thromboembolic events of ≥ 5% who required pacemaker or defibrillator surgery were randomized to continued-warfarin treatment or bridging therapy with heparin. The primary outcome was clinically significant device-pocket hematoma, which occurred in 12 of 343 patients (3.5%) in the continued-warfarin group as compared with 54 of 338 (16.0%) in the heparin-bridging group. There was one episode of cardiac tamponade and one myocardial infarction in the heparin-bridging group and one stroke and one TIA in the continued warfarin group. This study was stopped early after interim analysis found that the primary outcome occurred four times as often in the heparin-bridging group. These findings suggest that a strategy of continued warfarin therapy at the time of pacemaker or defibrillator surgery markedly reduced incidence of clinically significant device pocket hematoma as compared with heparin bridging (*N Engl J Med* 2013;368:2084-2093). ■

Pfizer launches own Viagra website

Pfizer is aggressively pursuing the online market for sildenafil (Viagra) by launching its own "Viagra home delivery" website. The drug will be available online directly from Pfizer but will still require a doctor's prescription. This move is also designed to counter online marketing of counterfeit Viagra, the most commonly counterfeited drug in the world. Pfizer plans to make Viagra available online at approximately $25 a pill. Meanwhile, the company has lost patent protection for its other version of sildenafil citrate marketed for pulmonary hypertension under the trade name Revatio. This version of the drug is only available in 20 mg strength, but is otherwise identical to Viagra, which is available in 25, 50, and 100 mg strengths. It is yet to be seen whether physicians will prescribe generic 20 mg sildenafil off label for erectile dysfunction. ■

Azithromycin and cardiovascular risk

Does azithromycin increase cardiovascular (CV) risk? A recent observational study showed that azithromycin was associated with a 2-3 times higher risk of death from CV disease in patients at high risk for CV disease (*N Engl J Med* 2012;366:1881-1890). A new study looks at the risk of the drug vs placebo and a comparator antibiotic (penicillin V) in Danish adults ages 18-64. As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of CV death (rate ratio 2.85; 95% CI, 1.13-7.24); however, when compared to penicillin V, there was no increased risk (crude rate CV death 1.1/1000 person years azithromycin vs 1.5/1000 penicillin V). With adjustment for CV risk, current azithromycin use was not associated with increased risk of CV death compared with penicillin V in a general population of young and middle-aged adults. (*N Engl J Med* 2013;368:1704-1712). This study is reassuring, suggesting that the increased risk of death is probably due to the illness rather than the drug, especially in low-risk populations. However, the risk of the macrolides still should be considered among patients with a high baseline risk of CV disease. ■

FDA actions

The FDA has approved a new once-daily combination inhaler for the treatment of chronic obstructive pulmonary disease (COPD). The product combines the long-acting beta-agonist (LABA) vilanterol with the steroid fluticasone furoate. Vilanterol is a new LABA and fluticasone furoate is reported to have longer lung retention time compared to the proprionate allowing for once-daily dosing. The product is a dry powder that is delivered via the Ellipta device. The new inhaler was evaluated in 7700 patients with COPD and showed improved lung function and reduced exacerbations compared to placebo. Vilanterol/fluticasone furoate is marketed by GlaxoSmithKline in collaboration with Theravance as Breo Ellipta.

The FDA has approved a new cholesterol combination drug, combining ezetimibe and atorvastatin. The drug is indicated for lowering cholesterol in patients with primary or mixed hyperlipidemia and in those with homozygous hypercholesterolemia. It is approved in four strengths, each containing 10 mg of ezetimibe with 10, 20, 40, or 80 mg of atorvastatin. The combination reduces LDL cholesterol levels up to 61% in clinical trials. Like the previously marketed simvastatin/ezetimibe, there is no evidence that the combination improves cardiovascular outcomes over a statin alone. The combination will be marketed by Merck as Liptruzet. ■