



MENOPAUSE CARE UPDATES

Released September 15, 2015

Menopause Care Updates presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause and healthy aging. Each review has commentary from a recognized expert that addresses its clinical relevance. Oversight for this e-newsletter was by Nancy Jasper, MD, FACOG, NCMP, Chair-elect of the 2015 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Jasper.

Innovations in the management of gallbladder disease

Baron TH, Grimm IS, Swanstrom LL. Interventional approaches to gallbladder disease. *N Engl J Med*. 2015;373(4):357-365.

Summary. Several interventional approaches to the management of gallbladder disease are described and analyzed in this review article by Baron and colleagues.

Surgical overviews include discussion of laparoscopic cholecystectomy, the removal of the gallbladder using minimally invasive laparoscopic techniques. Also discussed is a more recently developed surgical technique, natural orifice transluminal endoscopic surgery (NOTES), in which the surgeon accesses the gallbladder by using an endoscope that enters the body through a naturally occurring opening such as the mouth, vagina, or anus, thus requires no incision.

Percutaneous cholecystostomy, an option available for patients who are not candidates for the laparoscopic approach, is a technique that involves puncture of the gallbladder using ultrasound or computed tomography guidance. External tubes are employed for drainage. Gallstones may be extracted through the tubing and obviate the need for surgery.

Peroral endoscopic gallbladder drainage procedures are similar to percutaneous cholecystostomy, but differ in the type of tubing and can be performed using either the transpapillary route or the transmural route. Both routes involve the use of stents for drainage, but the most recent approach is endoscopic transmural drainage, which uses Doppler imaging for catheter or stent positioning.

The decision on which procedure to use depends on the severity of the disease, the patient's overall health, and available expertise and technology.

Commentary by



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Gallbladder disease occurs twice as frequently in women as in men. Risk factors for gallstones include obesity, increased parity, weight loss diets, bariatric surgery, and oral estrogen use. Specifically, oral contraceptives

and oral menopausal hormone therapy (HT) increase biliary cholesterol saturation, a prerequisite for cholesterol gallstone formation.

In the Women's Health Initiative, combined estrogen-progestogen therapy was associated with an increased absolute risk of 27 cases of gallbladder disease per 1,000 women after 5.6 years' use, whereas estrogen-only therapy resulted in an increased absolute risk of 45 additional cases per 1,000 women after 7 years.¹ The risk of gallbladder disease associated with HT appeared greater with oral rather than with transdermal estrogen use. For women who have gallstones or a history of gallbladder disease, HT should be administered with caution, and the increased risk of gallbladder disease should be included in discussions of the risks and benefits of HT.

Women health prescribers of oral estrogen or oral contraceptives need to remember the warning signs for gallbladder disease, which include abdominal pain, nausea, vomiting, fever, jaundice, dark urine, and light stools. Once acute cholecystitis is diagnosed, the most important considerations in selecting an approach are the patient's overall medical condition and the local and systemic consequences of the disease. Traditional laparotomy and primarily laparoscopic surgeries are used for cholecystectomy in these cases, with percutaneous drainage reserved for patients who are more ill.

In 2005, the Society of American Gastrointestinal Endoscopic Surgeons and American Society of Gastrointestinal Endoscopy formed a working group known as the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR)² and developed the term NOTES (natural orifice transluminal endoscopic surgery) for surgery performed using endoscopic instruments in the peritoneal cavity but gain access through a natural orifice rather than percutaneously.

NOTES is a rapidly evolving field within GI surgery in which the surgeon accesses the

peritoneal cavity via a hollow viscus and performs diagnostic and therapeutic procedures. Endoscopic approaches have included transgastric, transcolonic, transvaginal, and transurethral/transcystic.

The ultimate goal of NOTES is to eliminate the laparoscopic component altogether and perform surgery with access provided by "natural orifices," including the mouth, the vagina, the anorectum, or the urethra, based on the belief that a "hole" in a viscus is better tolerated than one in the abdominal wall.³

Potential benefits include elimination of an external scar and less ileus, pain, adhesions, or hernias compared with traditional laparoscopic surgery, with the potential of improved access to areas of the peritoneum for the severely obese and possibly shorter hospitalizations.⁴ Potential risks include infection, including bacterial contamination, peritonitis, or abscess formation; higher rates of peritoneal inflammation; and more difficulty dealing with major intraoperative complications such as bleeding with limited access approaches.⁵

Vaginal surgery with organ retrieval through the flexible vagina has been performed for many years, and closure of the vagina is less complex than other entry sites.⁶ Because transvaginal surgery has been identified as one of the natural orifices, women's health practitioners need to understand the philosophy behind NOTES and the potential risks and benefits of these approaches because its relative safety makes it a candidate for GI specialists wishing to remove gallbladders through the vagina.

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Disclosure: Dr. Pinkerton reports no relevant conflicts of interest.

Retail clinics, urgent care centers—new models of healthcare

Chang JE, Brundage SC, Chokshi DA. Convenient ambulatory care—promise, pitfalls, and policy. *N Engl J Med.* 2015;373(4):382-388.

Summary. Visits to ambulatory care settings account for approximately one-third of US healthcare spending. Most of these visits take place in office-based clinics and emergency departments; however, a growing number of patients are seeking care in retail clinics and urgent care centers, part of the “convenient care” industry providing fast, easily accessible, and more affordable care.

Retail clinics are walk-in health clinics typically located in pharmacies or supermarkets that provide immediate care for a narrow scope of services as well as some preventive care and care for chronic conditions. Urgent care centers are also walk-in health centers, but they treat a wider range of acute conditions requiring immediate but not emergency care.

However, several physician organizations have expressed concerns about the potential for convenient ambulatory care to fragment care and provide lower-quality care. Several states are considering legislation around the practice.

In this health policy report, Chang and associates characterize retail clinics and urgent care centers; examine their effect on cost, quality, access, patient navigation, and continuity of care; discuss existing standards

and regulatory approaches; and suggest policy considerations for balancing support for these new care models with essential protections for patients.

Commentary by



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Many of us seem to be in a time crunch, and our culture has shifted toward expecting rapid gratification. We order a pair of sandals on Amazon and expect quick fulfillment in 1 to 2 days—perhaps delivery not by UPS but in the near future by a drone. Our 10-year-old needs a sports physical, but we can’t get an appointment with the doctor for 3 weeks—why not go into a walk-in health clinic at Walgreens and get it done this evening after work? Thus, the patience element even for medical care has shifted.

This overview article by Chang and colleagues highlights several of the rapid changes taking place in our medical care system. To the consumer, these desirable changes appear to be convenient, are price transparent, provide easy access, and seem no different than walking into a restaurant for service. This economic market approach to low acuity episodic care embraced by businesses such as CVS, Walgreens, Target, Walmart, and Kroger are expanding the walk-in clinic footprint.¹

For the beleaguered primary care providers, what are some of the concerns aside from the competition for services? The walk-in clinics are staffed by lower-cost nurse practitioners and physician assistants, with extended daytime and some weekend hours. The health care provided is usually basic screening, diagnosis, and low-acuity conditions guided by standard clinical

protocols, and thus, we are perhaps less concerned about initial quality. However, as this business model gains traction and corporate profits increase, there is a trend toward expanding the scope to include chronic disease management such as diabetes, hypertension, and chronic obstructive pulmonary disease.²

Addressing these latter conditions begins to encroach on population health management, an area that requires a robust medical record platform, more complex protocol-driven approaches, greater training of clinical providers, continuity of care, appropriate referral, and oversight by primary- or subspecialty-trained physicians to the quality of health services and their outcomes. Will these investments be made?

Regulatory policies by the Joint Commission on Accreditation of Healthcare exist for urgent care clinics³; however, oversight for walk-in health clinics that pursue this more ambitious care model is lacking. The American Medical Association has provided a basic policy for in store walk-in health clinics,² but consistent, uniform medical regulatory policies are lacking.

The economic pie for medicine is large, and the “business” of medicine is rapidly changing. The emerging in-store walk-in clinic model will make an impact in our primary care landscape, and it is up to us the physicians and professional organizations such as the American Medical Association, The North American Menopause Society, and the American Congress of Obstetricians and Gynecologist to monitor and help shape these changes and advocate for the health our patients.

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Regional nodal irradiation after breast cancer surgery—survival, recurrence outcomes

Whelan TJ, Olivotto IA, Parulekar WR, et al; the MA.20 Study Investigators. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373(4):307-316.

Burstein HJ, Morrow M. Nodal irradiation after breast-cancer surgery in the era of effective adjuvant therapy [editorial]. *N Engl J Med*. 2015;373(4):379-381.

Summary. To study whether the addition of regional nodal irradiation to whole-breast irradiation improved outcomes after breast-conserving surgery, 1,832 women with node-positive or high-risk node-negative breast cancer treated with breast-conserving surgery and adjuvant systemic therapy were randomly assigned to either whole-breast irradiation plus regional nodal irradiation (nodal-irradiation group; n=916) or whole-breast irradiation alone (control group; n=916). Overall survival was the primary outcome; secondary outcomes were disease-free survival, isolated locoregional disease-free survival, and distant disease-free survival.

At the 10-year follow-up, there was no significant between-group difference in survival, with a rate of 82.8% in the nodal-irradiation group and 81.8% in the control group (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.72-1.13; $P=.38$). Rates of disease-free survival were 82.0% and 77.0%, respectively (HR, 0.76; 95% CI, 0.61-0.94; $P=.01$), and 10-year rates of isolated locoregional disease-free survival were 95.2% and 92.2%, respectively (HR, 0.59; 95% CI, 0.39-0.88; $P=.009$).

Among women with node-positive or high-risk node-negative breast cancer, adding regional nodal irradiation to whole-breast irradiation did not improve overall survival but reduced the rate of breast cancer recurrence.

Commentary by



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Radiotherapy to the chest wall and regional lymph nodes is commonly used after mastectomy in women with node-positive breast cancer who are treated with adjuvant systemic therapy. It is known to reduce both locoregional and distant recurrences, and it improves overall survival.

Postmastectomy radiotherapy has been shown to improve survival for women with one to three affected axillary lymph nodes but only in the context of a 5-year local-regional recurrence rate of 17% that is far in excess of current rates.¹ An unanswered question had been whether the addition of regional nodal irradiation to whole-breast irradiation after breast-conserving surgery has the same effect.

Most of the patients in this study received systemic combination chemotherapy that included an anthracycline or a taxane, along with endocrine therapy in three-fourths of the women. It is not clear which sites of nodal irradiation (internal mammary, supraclavicular, level III axillary, or all three) led to improvements in disease-free survival.

Importantly, the rates of distant disease-free survival at 10 years were nearly 4% higher in the radiated group, a modest improvement. Although there were no increases in the rates of brachial neuropathy, cardiac disease, or secondary cancers in the nodal-irradiation group, the period of follow-up was not sufficiently long to rule out a difference in the rate of secondary cancers. There was a near doubling (absolute increase, 4%) in the rate of

lymphedema among patients who were treated with regional nodal irradiation. The rate of acute radiation pneumonitis was significantly higher in the nodal-irradiation group, although the condition was uncommon in the two groups.

Most of these women were treated years ago. The reported results may be greater than would be expected for patients treated today because these results incorporated radiation and systemic-therapy standards that were in use when the patients were treated as long as 15 years ago that did not universally include current systemic treatments, such as taxanes, trastuzumab, and more effective endocrine strategies, now known to reduce local recurrence and improve survival. The limited axillary surgery used in the study might also have contributed to the observed benefit of regional nodal radiation. In contrast to these results, for example, the Comparison of Complete Axillary Lymph Node Dissection With Axillary Radiation Therapy in Treating Women With Invasive Breast Cancer (AMAROS) trial involving patients who had undergone axillary dissection after positive results on sentinel-lymph-node biopsy, a median of 17 nodes were removed, and 5-year rates of regional recurrence without regional radiotherapy were less than 0.5%.²

Sentinel-lymph-node biopsy without axillary dissection is being performed today in many more patients with sentinel-node-positive disease, and for most patients, the risks of local-regional recurrence after breast surgery are now extraordinarily low, typically less than 5% during 10 years of follow-up. With the use of clinical-pathological characteristics to offer postmastectomy radiotherapy selectively, 5-year local-regional recurrence rates of 3% to 4% without radiotherapy are now observed, and most women are able to avoid radiotherapy

Today, regional nodal irradiation for patients with one to three lymph-node metastases is probably appropriate only for patients with other adverse prognostic factors, such as age younger than 50 years, extensive lymphovascular

invasion, a high histologic grade, an unfavorable molecular profile, or primary tumor size of more than 5 cm. The relatively modest benefits of nodal irradiation, coupled with a small chance of serious toxicity in women with metastases in one to three axillary nodes, emphasize the importance of additional studies to examine more individualized treatment strategies.

A number of published studies suggest that prognostic and predictive genomic profiling can be a more reliable predictor of local recurrence than tumor stage or other traditional clinical factors and hence holds the promise for more refined approaches to regional radiotherapy. Because the absolute benefit of regional nodal radiation was modest and associated with rare but potentially serious adverse events, these findings show the importance of basing treatment decisions on a careful discussion of the potential benefits and risks with each patient.

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Disclosure: Dr. Vogel reports no relevant conflicts of interest.

Atrophic vaginitis diagnosis on Pap test versus physical examination

Heller DS, Weiss G, Bittman S, Goldsmith L. Does a diagnosis of atrophic vaginitis on Papanicolaou test signify the presence of inflammation? *Menopause*. 2015;22(8):814-815.

Summary. Loss of estrogen in menopause leads to vaginal changes that show on a Papanicolaou (PAP) test, with a shift in maturation index to

more parabasal cells. Researchers conducted a retrospective review of Pap test slides from University Hospital Newark to see whether a cytologic diagnosis of atrophic vaginitis is a reliable indicator of histologic inflammation.

Cases that had been diagnosed as either atrophic vaginitis (n=100) or atrophic pattern (n=100) were selected. Slides were then re-reviewed and scored based on the abundance of neutrophils. Data were assessed for trend to determine associations between the proportion of women with a histologic diagnosis of atrophic vaginitis and increasing numbers of neutrophils. A diagnosis of atrophic vaginitis on a Pap test was significantly associated with increased numbers of neutrophils; atrophic pattern was indicative of low numbers.

The researchers believe that because the Pap test diagnosis of atrophic vaginitis does not correlate with clinical symptoms, a single diagnostic term that does not suggest a disease state would more reliably communicate cytology findings to clinicians.

Commentary by



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Heller and associates pose an interesting question in their recent paper in the journal *Menopause* that their methods of reviewing PAP slide results allowed them to answer. Whether read by a cytologist or by a physician, the diagnosis of atrophic vaginitis was accompanied by greater than 10 neutrophils per high-power field in 75% of cases, implying inflammation.

However, one very important issue to the treating clinician that the authors addressed is

that there is no correlation with the patient's symptoms.

Pap tests can provide three specific diagnoses:

1. Vaginal atrophy (increased parabasal cells)
2. Vaginal atrophy without inflammation (no significant increase in neutrophils)
3. Vaginal atrophy with inflammation (significantly increased neutrophils)

None of these informs about the need for treatment. The necessity for treatment depends on the symptoms of the individual patient and the clinician's observations on physical examination.

Pap tests are clearly not helpful for diagnosis or treatment of this entity. More helpful is to ascertain whether the complaints of the patient plus the examination fit the new definition of the genitourinary syndrome of menopause (GSM), implying that appropriate treatment is necessary.¹

The author's suggestion that a new single term for the Pap test reflective of hormonal status when dealing with the menopausal patient is probably unnecessary.

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Disclosure: Dr. Nachtigall reports no relevant conflicts of interest.

In Other News

NAMS presents summaries of other recently published articles for your review

Nitroglycerin for hot flashes

Huang AJ, Cummings SR, Schembri M, Vittinghoff E, Ganz P, Grady D. Continuous transdermal nitroglycerin therapy for menopausal hot flashes: a single-arm, dose-escalation trial [published ahead of print August 8, 2015]. *Menopause*.

Clinical studies have shown that nitric oxide (NO) plays a role in mediating peripheral

vasodilation during hot flashes. One pharmacologic agent with direct effects on NO-mediated vasodilation is nitroglycerin. Nineteen perimenopausal and postmenopausal women (mean age, 51.4 y) reporting at least seven hot flashes per day were recruited into a dose-escalation trial of continuous transdermal nitroglycerin. Over 4 weeks, participants escalated dosage weekly from 0.1 mg per hour to 0.2 mg, 0.4 mg, or 0.6 mg per hour, then discontinued nitroglycerin during the final week. Changes in hot flash frequency and severity were assessed using symptom diaries. The average daily frequency of hot flashes decreased by 54% and of moderate to severe hot flashes by 69% from baseline to maximum-dose therapy. After discontinuing nitroglycerin, participants reported an average 23% increase in frequency of any hot flashes and 96% increase in moderate to severe hot flashes, suggesting that continuous nitroglycerin may have a role in decreasing hot flash frequency and severity.

Testosterone levels associated with depression in white menopausal women

Milman LW, Sammel MD, Barnhart KT, Freeman EW, Dokras A. Higher serum total testosterone levels correlate with increased risk of depressive symptoms in Caucasian women through the entire menopausal transition. *Psychoneuroendocrinology*. 2015;62:107-113.

In a longitudinal cohort study (428 women), using data from the Penn Ovarian Aging Study, serum hormone levels and depression scores using the Center for Epidemiological Studies of Depression scale (CES-D) were measured at annual visits over a 14-year period.

Serum total testosterone levels increased progressively over the study period and were associated with older age and current smoking. Total testosterone levels were significantly higher in postmenopausal African American women compared with Caucasian women ($P=.012$). The proportion of women with a CES-D score of 16 or less significantly decreased with increasing age and in the postmenopausal period and were higher in women with a history of depression and hot

flashes. In Caucasian women, but not in African American women, higher serum testosterone levels were associated with increased depressive symptoms after controlling for several variables including age, obesity status, hot flashes, and menopause status (relative risk, 1.09; 95% confidence interval, 1.00-1.17; $P=.042$). In addition to age and history of depression, race was identified as having a significant interaction between the association of testosterone levels and depressive symptoms.

Menopause Editor's picks for September 2015

NAMS spotlights selections from the most recent issue of the Society's official journal, *Menopause*, chosen by its editor in chief, Isaac Schiff, MD.

Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women

JoAnn V. Pinkerton, MD, and Nanette Santoro, MD



Facilitating lifestyle changes to manage menopausal symptoms in women with breast cancer: a randomized controlled pilot trial of The Pink Women's Wellness Program

Debra J. Anderson, PhD; Charrlotte Seib, PhD;
Alexandra L. McCarthy, PhD; Patsy Yates, PhD;
Janine Porter-Steele, MNS; Amanda McGuire, MNS;
and Leonie Young



Long-term follow-up of bone density in women with primary ovarian insufficiency

Cristina L. Benetti-Pinto, MD, PhD; Valeska B. Ferreira;
and Daniela A. Yela, MD, PhD



Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone)

David F. Archer, MD; Fernand Labrie, MD, PhD;
Céline Bouchard MD; David J. Portman, MD;
William Koltun, MD; Leonello Cusan, MD, PhD;
Claude Labrie, MD, PhD; Isabelle Côté, BSc, CCRP;
Lyne Lavoie, MSc; Céline Martel, PhD; John Balsler,
PhD; and other participating Members of the VVA
Prasterone Group



Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality

Tomi S. Mikkola, MD, PhD; Pauliina Tuomikoski, MD,
PhD; Heli Lyytinen, MD, PhD; Pasi Korhonen, PhD;
Fabian Hoti, PhD; Pia Vattulainen, MSc; Mika Gissler,
MSocSci, PhD; and Olavi Ylikorkala, MD, PhD

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