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INSIDE

Non-Invasive Prenatal Diagnosis Screening

ABSTRACT & COMMENTARY

Non-invasive prenatal diagnostic screening has become a hot topic of late. Large studies from England, Europe, and now 2 from the United States have borne out the efficacy of first trimester ultrasound determined nuchal translucency (NT) testing, with or without additional information provided by first trimester biochemical analysis (beta-hCG and PAPP-A).[1-4] Now the data from one of these NICHD-funded studies [First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN)] have been published regarding the usefulness of adding a second trimester triple screen to the diagnostic mix.

Platt and colleagues tracked 4,325 patients of the original 7,392 patients having first trimester NT and biochemical screening who elected to have second trimester testing through triple screening (total hCG, unconjugated estriol, and alpha-fetoprotein). In this study, 4,145 patients had a negative first trimester screen and 180 had a positive first trimester screen (> 1:270).

In the 4,325 first trimester screen negative sample, there were 7 fetuses with trisomy 21, 6 of whom were picked up by the second trimester biochemistry. All 7 cases of trisomy 21 that were in the screen-positive group were also identified with the second trimester biochemistry, but there was a screen-positive rate of 38% in this group. Platt et al found that by using both first and second trimester testing together in this way (the sequential method) a sensitivity of 98% could be attained with a cut-off for trisomy 21 of 1:270 at an overall false positive rate of 17% (Platt LD, et al. *Obstet Gynecol*. 2004;104(4):661-666).

COMMENT BY JOHN C. HOBBINS, MD

Over the past 5 years various combinations of prenatal testing for Down syndrome have emerged: 1) ultrasound assessment of NT alone (with or without evaluation of the fetal nasal bone; 2) combined—NT and first trimester biochemistry; 3) integrated—NT, first trimester biochemistry and second trimester quad screen (hCG, E3, MSAFP, and Inhibin-A); and now 4) sequential—as described above. The difference between the integrated method and the sequential method is simply that with the former only one risk figure is generated which is only

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available to the patient after the results of the second trimester biochemistry are in. With the sequential approach each patient will get 2 sets of results: one at the end of the first trimester and another a short time after the second trimester blood is drawn. The advantage of the sequential method is that the patient can weigh her options at least 2½ weeks earlier than the patient enrolling in the integrated program. The theoretical advantage of the integrated screen is that it is more sensitive than the sequential while generating fewer false positives.

It is interesting that some individuals initially challenged the ethics of the soon to be published First and Second Trimester Evaluation of Risk Trial (FASTER) trial in which information about the thickness of the NT and the biochemistry was withheld until the second trimester data had been folded into the results. In fairness, however, if cystic hygromas or large NT's were found in the FASTER study, the patient was immediately notified at the time of the ultrasound scan. Also, when the study was initiated, the compelling data from Britain was not matched by results from the only US study at the time which had a sensitivity of 33%, compared with the NT data from the Landmark British Trial, suggesting a sensitivity > 75%. The FASTER study represented a way to independently assess in an American population the true sensitivity of NT testing with well-trained operators using compulsively standardized methods. Fortunately, this study and the BUN investigation have yielded information that is very similar to the British group's data.[5,6]

Now patients have a variety of options available to them, which, hopefully, can be laid out in a way that is reasonably easy to understand (despite the nuances involved). We have not even touched upon the role a genetic sonogram might play as either an additional diagnostic adjunct or as a substitute for, let's say, second trimester biochemistry. The obvious benefit would be to identify non-chromosomal anomalies and those forms of aneuploidy, such as trisomy 13, which might not be screened in by the above testing regimens. Data from patients in the FASTER trial suggest that the genetic sonogram also will pick up the remaining trisomy 21's not screened in with NT and first and second trimester biochemistry testing.

The goal of all non-invasive testing, which seems to be close to being met, is to limit the need for chorionic villus sampling and amniocentesis to a minimum while re-assuring with reasonable accuracy the overwhelming majority of patients that their risk of having a fetus with trisomy 21 is substantially lower than the risk of invasive testing. ■

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Does Practice Make Perfect?

ABSTRACT & COMMENTARY

Synopsis: *Physicians who have been practicing longer may be at risk for providing less quality care.*

Source: Choudhry NK, et al. *Ann Intern Med*. 2005;142: 260-273.

CHOUDHRY AND COLLEAGUES SOUGHT TO ESTABLISH the relationship between quality of care with clini-

cal experience by reviewing 62 articles that measured physician knowledge or quality of care as well as time since medical school graduation or age. More than 50% of the studies suggested that physician performance actually declined while only 1 study showed improved performance. The areas measured in the various studies included: knowledge; adherence to standards of practice for diagnosis, screening, and prevention; adherence to standards of appropriate therapy; and outcomes.

Choudhry et al acknowledge that there are potential limitations to the study, each of which could explain aspects of the findings. For example, there may be other studies that were missed in the review of the literature showing the opposite findings, but there is no reason to believe that a significant number of those exist. Similarly, since the studies were not designed to specifically look at the relationship between experience and outcomes, these could be chance findings, but since the findings were very consistent, this explanation is unlikely. As a third explanation, Choudhry et al suggest that differences between practice guidelines could make *standard of care* a difficult measurement to establish. Analysis of the data did not support this view. Finally, the potential benefit of practice experience might be measured in parameters not covered here, such that its positive effects would not be apparent here. Since the measurements used seem to cover the gamut of how physician performance is usually assessed, this certainly cannot be disproven, but lacks credibility.

COMMENT BY FRANK W. LING, MD

Before you skip past this review as irrelevant, consider its implications. Nobody (the authors, myself, or anyone else) is saying that you, specifically, are providing a lower quality of health care than your younger peers. These data are all about large groups of physicians. Neither do the data tell us that younger physicians are better than their older, more seasoned peers. If you are wondering what specialties were involved in the studies reviewed, you should know that these were not just internists and, in fact, there were several studies which included obstetrician/gynecologists. The concern is both at the individual practitioner level as well as for medicine as a whole. Continuing medical education is under the gun here, as is the ongoing certification process. In order for the public to receive optimal healthcare, how do I individually, and we, collectively, address these findings?

Without question, I've got to look at my own practice patterns. Am I aware of current evidence-based recommendations and guidelines? Do I practice the way I was trained as a resident or based on what I heard from a single speaker at a meeting several years ago? Do I rely on more widely accepted recommendations offered by respected organizations that have done systematic reviews of the data? Do I keep up with current literature, whether by reading journals or through summaries in publications such as *OB/GYN Clinical Alert*? Do I track my patient outcomes to look at problems that I need to address better?

Maybe these questions are answered more comfortably by someone who has recently completed training and has that *little voice* of their teachers asking nagging questions of them. Indeed, their database should be more current, albeit inexperienced. Certainly as my own hair whitens and thins, I am constantly reminded of the ever-changing technology and exploding knowledge base that I face. Having been in full-time private practice now for a full year, I am painfully aware of the challenges that I face trying to keep up. What I don't ever want to do, however, is to only fall back on my years of experience at medical school and assume that is sufficient for the years ahead of me in practice. I would challenge the reader to do the same: keep this article in mind as you continue to provide your patients with the best care possible. Let's maximize the effectiveness of our CME time, let's help the hospitals and insurance companies with their quality improvement plans, and let's do the best we can for our patients, regardless of how long we've been out of training. ■

Does It Matter How Ovaries Removed Prophylactically Are Processed Pathologically?

ABSTRACT & COMMENTARY

Synopsis: *A rigorous operative and pathologic protocol for RRSO increases the detection rate of occult ovarian malignancy in BRCA mutation carriers nearly sevenfold. If confirmed, this finding will alter postoperative management because additional staging, chemotherapy, and follow-up may be necessary in affected women.*

Source: Powell B, et al. *J Clin Oncol*. 2005;23:127-132.

It has been consistently demonstrated that women with deleterious BRCA1 and BRCA2 mutations have an increased lifetime risk for ovarian cancer, prompting some to consider prophylactic adnexectomy

after childbearing. While not completely protective, the procedure appears to reduce incident risk significantly. In addition, it has been documented that a small proportion of these removed ovaries harbor occult malignancy, a finding that provoked Powell and colleagues to institute a specific specimen processing protocol for ovaries removed under the indication of prophylactic adnexectomy. The principal deviation from standard protocol was 2-mm serial sectioning in the removed adnexal structures (tube and ovary) combined with random biopsies and cytology. From 118 probands and female relatives, 67 patients (57%) had pathological material and operative records for analysis. In 41 of these cases (61%) the protocol was followed fully or partially. In total, 7 cancers were identified—all within the group for whom the protocol was followed (17% of protocol patients). None were identified among the 26 cases processed by standard methods. This strong effect of the protocol in cancer identification was independent of other variables such as age, BRCA1 or BRCA2 mutation, or type of surgery. Powell et al concluded that rigorous pathological sampling will identify more patients with occult malignancy, and suggested the reported detection rate among high-risk women is likely underestimated.

COMMENT BY ROBERT L. COLEMAN, MD

"The more you look, the more you find. . ."—a phrase true to the dictum of sampling. It should not come as a surprise that more thorough investigation would identify more disease, particularly if these lesions were typically occult. However, time, cost, and resource constraints limit our ability to follow this practice on all specimens removed at the time of surgery. In the case of geneticallly high-risk women undergoing prophylactic surgery, prevalence of disease would support the resource allocation. There are other examples where extended sampling, as well as other procedures, now accompanies the evaluation of a high-profile specimen. One good example is the evaluation of a sentinel node. This specimen is characterized and identified intraoperatively as the first and highest at-risk node draining a primary tumor. Prevalence of disease is by definition highest here. Validation of this hypothesis has now mandated serial sectioning in most cases as well as adjuvant immunohistochemistry and PCR-based analysis in some situations searching for the earliest evidence of metastatic spread. The difficulty in practice is what to do with the information when it is found.

It is likely that most of the women with occult primary disease identified by serial sampling in the current study will be salvaged by surgery with or without indicated adjuvant chemotherapy. The question remains as to what degree adjunctive procedures should be performed in the absence of gross tumor. Should all patients undergo peritoneal sampling with an omentectomy? Should a lymphadenectomy be performed given that 10%-20% of the patients in this cohort will have a malignancy? Currently, justification for formal staging of borderline ovarian tumors is supported on a similar incidence of up-classifying the disease to invasive malignancy. Validation of these additional and potentially invasive procedures is necessary prior to formal guidelines.

Previous studies have suggested that both the ovary and fallopian tubes are tissues of increased risk in patients with BRCA mutations. This trial adds to the growing body of data in this regard as 4 of the 7 identified abnormalities were fallopian tube in origin. Concern for complete tubal resection in these patients has prompted some to also recommend hysterectomy in order to insure the cornual section of the tube is removed as well. The addition of this procedure will likely increase the potential for morbidity, necessitating the conduct of future prospective trials to clearly demonstrate its benefit in the care of these patients. Currently, hysterectomy is more strongly advocated among women undergoing risk-reducing surgery because of family or personal history of hereditary non-polyposis colorectal cancer.

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The WHI Results on Urinary Incontinence

ABSTRACT & COMMENTARY

Synopsis: *Conjugated equine estrogen alone and CEE + MPA increased the risk of urinary incontinence among continent women and worsened the characteristics of urinary incontinence among symptomatic women after 1 year.*

Source: Hendrix SL, et al. *JAMA*. 2005;293:935-948.

RESULTS FROM THE 2 CANCELED ARMS OF THE Women's Health Initiative (WHI) were reported for the presence of urinary incontinence after one year of treatment in those women without incontinence at baseline and for the severity of urinary incontinence in those

who reported incontinence upon entry to the study. **Findings were as follows:**

	Estrogen+Progestin	Estrogen Alone
Women asymptomatic At baseline:		
Any incontinence	1.39 (1.27-1.52)	1.53 (1.37-1.71)
Stress incontinence	1.87 (1.61-2.18)	2.15 (1.77-2.62)
Urge incontinence	1.15 (0.99-1.34)	1.32 (1.10-1.58)
Older women and women most distant from menopause were at greater risk, but the confidence intervals were wider because of smaller numbers:		
Age 70-79	2.24 (1.17-4.30)	2.63 (1.32-5.25)
Worsening in women with Incontinence at baseline:		
Any incontinence	1.20 (1.06-1.36)	1.59 (1.39-1.82)

The use of hormone therapy for longer periods of time was examined in an 8.6% subset on treatment for 3 years, and there did not appear to be any meaningful changes in the relative risks.

COMMENT BY LEON SPEROFF, MD

This contribution from the WHI does not disagree with the overall results in previous literature. All of these results have been contrary to what seemed like a logical conclusion, that estrogen treatment would reduce or prevent incontinence by improving or avoiding the atrophy of the genito-urinary tract that follows menopause.

It has been argued that genuine stress incontinence is not affected by treatment with estrogen, whereas others have contended that estrogen treatment improves or cures stress incontinence in more than 50% of patients due to a direct effect on the urethral mucosa.[1-3] However, a meta-analysis concluded that improvement was reported only in nonrandomized studies.[4] Two randomized trials dedicated to this clinical problem failed to demonstrate a beneficial effect of estrogen treatment.[5,6] Most cases of urinary incontinence in elderly women are a mixed problem with a significant component of urge incontinence that clinicians believed to be improved by estrogen therapy. However, the Heart and Estrogen-progestin Replacement Study (HERS) randomized trial indicated a worsening of incontinence with hormone therapy for both urge and stress incontinence, and the Nurses' Health Study reported a small increase of incontinence in hormone users.[7,8]

These results seem somewhat surprising, and indicate that the mechanism for stress incontinence is not only unresponsive to estrogen's beneficial effects on epithelium, but even worsened. Although the adverse effects were more prominent in the oldest women in the WHI, the impact was observed in younger women as well. This certainly challenges the urogynecologists to study this mechanism and understand the physiology behind these epidemiologic results.

One could nitpick this report from the WHI. For example, the participants in the 2 trials were not identical (more reported daily incontinence in the estrogen only arm, and the estrogen only arm had more elderly women), and current users of hormone therapy upon entry to the study did not have an adverse effect on incontinence (but the numbers were small). It is intriguing to wonder why the women who were currently using hormone therapy at baseline did not report this adverse effect. However, the overall results are consistent with the literature on this subject, and we should accept that postmenopausal hormone therapy carries a small increase in worsening or onset of incontinence. Most importantly, the reason why needs understanding. ■

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The Length of Third Stage of Labor and Risk of Postpartum Hemorrhage

ABSTRACT & COMMENTARY

Synopsis: *A third stage of labor longer than 18 minutes is associated with a significant risk of postpartum hemorrhage. After 30 minutes the odds of having postpartum hemorrhage are 6 times higher than before 30 minutes.*

Source: Magann EF, et al. *Obstet Gynecol*. 2005;105: 290-293.

How long does one wait for a placenta to deliver without help? A paper recently surfaced to answer that question. Magann and colleagues reviewed 2 hours worth of data from one hospital involving 6588 vaginal deliveries. These deliveries were attended by nurse midwives under guidelines that included watchful waiting during the third stage of labor until 30 minutes, after which an attempt was made to remove the placenta through manual extraction. The appealing feature of the study was that postpartum blood loss was compulsively assessed by use of collection devices and the weighing of linens. Magann et al defined postpartum hemorrhage (PPH) as a total maternal blood loss of > 1000 cc. Hemodynamic stability or drop in hematocrit were not used as dependent variables. The results were interesting in that the median third-stage times were only 2 minutes different between those experiencing PPH and those not having this complication (9 minutes vs 7 minutes). However, the results indicated that the longer the placenta stayed in, the greater the chance of PPH. The risk was significant at 10 minutes (OR, 2.1; 95% CI, 1.6-2.6). At 20 minutes the OR was 4.3 (95% CI, 3.3-5.5) and after 30 minutes, the OR was 6.2 (95% CI, 4.6-8.2).

COMMENT BY JOHN C. HOBBINS, MD

Others have reported that:

1. Significant PPH occurs in 4% of deliveries;[1]
2. Third stage length of more than 30 minutes has been associated with a significant increase in PPH;[2]
3. Although controversial, some have indicated that active management of the third stage (with ecbolics such as methergine or oxytocin, etc) results in shorter third stages and less blood loss compared with the passive approach.[3,4]

There were a few interesting wrinkles in the above study that might possibly affect its interpretation. For example, despite the usual hands-off approach by nurse midwives, oxytocin was given with the anterior shoulder (our practice is to routinely use a pitocin drip only after delivery of the placenta). Also, Magann et al state that the vast majority of deliveries were accomplished under epidural anesthesia and one wonders whether these results would apply to those not having epidurals.

The most puzzling part of the study has to do with an apparent discrepancy between the study protocol and the results. Supposedly placentas were all manually removed *after thirty minutes following delivery of the neonate*. However, the results showed a 6-times greater risk of PPH after 30 minutes and their 90th percentile started at 1 hour and 48 minutes. Since the median difference between groups was only 2 minutes, a few "maverick" values could be skewing the results.

It is clear from this study and others that the longer the placenta stays in the greater the chance of PPH. However, is it the presence of the unextracted placenta or the reason the placenta is retained that is responsible for the hemorrhage? Also, how large a role does our answer to retained placenta (manual extraction and D & C) play in the ultimate total blood loss? Is the solution actually the cause?

Retained placentas come in 3 varieties—those that are separated and are in the lower uterine segment or vagina; those that are separated but still in the uterus; and those that have not yet separated. Wherever they are, if they are separated, a gentle pull on the cord should suffice to deliver the placenta. If not, how long should we wait for the rare adherent one to separate? This dilemma lends itself to further investigation through simple ultrasound evaluation—something that is underway at our institution.

I have a feeling that the above study, with all its limitations, will start a dictum that at 18 minutes 30 seconds all placentas should be manually extracted. Worse yet, since after 10 minutes of third-stage labor the study showed a doubling of risk, even earlier aggressive interventions would now be entertained. This could then prompt the logical sequel on inverted uteri and PPH.

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Validating Intraoperative Pathology: Frozen Section

ABSTRACT & COMMENTARY

Synopsis: *The accuracy of frozen section diagnosis for the assessment of the ovarian mass is good, with acceptable sensitivities for almost perfect specificities. Future studies on patient preferences for the different outcomes, as well as economic analysis, are needed for definite position of this diagnostic technique.*

Source: Geomini P, et al. *Gynecol Oncol*. 2005;96:1-9.

The use of intraoperative frozen section for preliminary analysis of extirpated adnexal masses

is ubiquitous and appears to benefit our surgical practice in providing some modicum of comfort in cases where no malignancy is found and guidance to further staging when malignancy is identified. However, how accurate is it? Geomini and colleagues performed a metaanalysis from published studies to determine the accuracy of frozen section when conducted in the context of adnexectomy. Manuscripts appearing in the medical literature between 1966 and 2003 in which intraoperative frozen section diagnosis was compared to final pathologic diagnosis were reviewed. For each study, prevalence of disease (malignant and borderline) and diagnostic sensitivity and specificity was calculated using the final histologic diagnosis as a reference. Two by two tables were constructed; one assigning borderline tumor as benign and one as malignant.

Eighteen studies were included in the analysis. Sensitivity and specificity were 65-97% and 97-100%, respectively when borderline tumors were classified as malignant and 71-100% and 98-100%, respectively, when considered benign. The pooled estimate for specificity was over 99%. Significant heterogeneity precluded an accurate pooled estimate for sensitivity, which varied widely among the surveyed trials. The authors concluded that, in general, the accuracy of frozen section diagnosis was good and characterized by almost perfect specificity. Given the range of prevalent malignancy, discriminate use of the technique could be practiced with likely little overall detrimental impact to patient care. Future work with economic analysis is warranted.

COMMENT BY ROBERT L. COLEMAN, MD

I have to admit; the issue of validating the diagnostic accuracy of intraoperative frozen section is one I really never felt compelled to question scientifically. Since this is a diagnostic triage mechanism used by surgeons everyday, it would appear the limitations, risks and benefits are well understood, accepted, and validated in treatment planning. Indeed, part of the informed consent process entails a discussion of the anticipated surgical procedures surrounding the removal of an adnexal mass, which, are indirectly and directly based on the predictive capacity of the frozen section diagnosis. However, this paper represents another good example of questioning a routine practice in an effort to more clearly understand that which we base decisions upon.

It is reassuring that false-positive rates are quite low and reproducible across different centers; few patients will undergo unnecessary radical surgery based on over-diagnosing malignancy. However, it appears a more sizeable proportion of patients may inappropriately undergo an abbreviated adnexectomy in the presence of significant pathology (false negative). The rate at which this occurs was highly variable in the reviewed studies and may reflect significant biases of methodology and/or ranges in expertise for diagnosing ovarian pathology at frozen section. In either event, the impact of being wrong is an important consideration to quantify and scrutinize. Geomini et al approached this issue from a statistical standpoint; that is, using an interesting analytical probability model termed "regret." In this type of analysis, a relative value of being wrong in one's prediction of malignancy intraoperatively is calculated by a ratio of the two adverse outcomes. For example, a regret ratio (false positive/false negative) of 10 indicates a false positive result at frozen section would generate 10 times the regret as a false negative result. Using this model in a fictive cohort of 1000 patients undergoing frozen section, the authors demonstrate that in most cases frozen section is of value and reduces regret.

One statistical challenge of note in the presented analysis was the assignment of borderline tumors. Since $2 \cdot 2$ tables were needed to render hypothesis testing, a decision as to whether this condition was "benign" or "malignant" was required. In the analysis presented both were considered, which led to relatively little variance in the calculated sensitivities and specificities. However, in practical terms, frozen section analysis suggesting borderline pathology may be associated with malignancy in up to 30% of cases—particularly with mucinous tumors. This relatively high rate of "up-diagnosing" at permanent section usually causes the gynecologic oncologist to consider only the "not normal" allocation, rather than a specific diagnosis. The downside of being wrong (understaging a true malignancy) is over-treatment with chemotherapy. However, about 60% of frozen section diagnoses suggesting a borderline lesion are truly associated with that pathology. The intrinsic value of complete surgical staging in this situation is debatable but is still preferred by most gynecologic oncologists. The economic impact of clinical practice based on these accuracy determinations may help to improve the precision of intraoperative diagnosis. ■

Additional Reading

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2. Pinto PB, et al. *Gynecol Oncol*. 2001;81(2):230-232.
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CME Question

10. The following statements are true regarding postmenopausal hormone therapy and the risk of incontinence *except*:

a. Hormone therapy does not appear to benefit any specific type of incontinence.
b. Estrogen therapy does not increase incontinence in younger women closer to their menopause.
c. The adverse effect of hormone therapy was observed only in women who had incontinence to begin with.
d. Women who were currently using hormone therapy at entry to the study did not report the onset or worsening of incontinence.

Answer: 10 (a)

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Preparing for the Possibility of a Bird Flu Pandemic

The possibility of a bird flu pandemic has health officials worldwide in a high state of alert. The highly pathogenic avian influenza A virus is responsible for the death of more than 100 million birds in Southeast Asia, but less than 100 cases have been documented in humans, and only 2 of those have been from human-to-human contact. Still, influenza A viruses are known to undergo an antigenic shift periodically, marking an abrupt change in the viral genome. It is the possibility of a mutation that has health officials concerned. If the virus suddenly became infectious in human populations, the resulting pandemic could kill millions, as similar avian influenza virus pandemics did in 1968, with one to four million deaths, and 1918, when the avian flu pandemic killed as many as 50 million people. The World Heath Organization is urging all countries to develop or update their influenza pandemic preparedness plans. From a pharmaceutical perspective, the WHO has singled out oseltamivir (Tamiflu) as the treatment of choice to reduce symptoms and prevent spread of avian influenza. Roche Holding AG, the makers of oseltamivir, recently announced that Britain and the United States are discussing large purchases of the drug, with the intent of stockpiling supplies for a potential avian influenza outbreak. Other governments around the world have been stockpiling the drug as well, and Roche is increasing its production capacity to meet the additional demand.

Amoxicillin-Clavulanate vs Ciprofloxacin

The search for effective antibiotics to treat common infections is a high priority, given increasing resistance patterns for many commonly used antibiotics. This was the basis for a new study by researchers at the University of Washington, in which they compared ciprofloxacin to amoxicillin-clavulanate in women with uncomplicated cystitis. The study was driven by an increasing rate of resistance to trimethoprim-sulfa and other antimicrobials among *E. coli* strains causing acute cystitis in women. While ciprofloxacin is a common alternative, amoxicillin-clavulanate has not been well studied. In a randomized, single-blinded trial, 370 women aged 18 to 45 with symptoms of acute uncomplicate cystitis with a positive urine culture were randomized to amoxicillin-clavulanate 500/125mg twice daily or ciprofloxacin to 250 mg twice daily for 3 days. Clinical cure was observed in 58% of women treated with amoxicillin-clavulanate, compared with 77% of women treated with ciprofloxacin ($P < .001$). Amoxicillin-clavulanate was not as effective as ciprofloxacin, even among women infected with *E. coli* strains suscepti-

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ble to amoxicillin-clavulanate. At follow-up visits 2 weeks after treatment, 45% of women in the amoxicillin-clavulanate group had vaginal colonization with *E. coli*, compared to only 10% in the ciprofloxacin group ($P <$ .001). The authors point out that *E. coli* resistance is an increasing problem worldwide, especially with trimethoprim-sulfa. However, resistance is also been seen with fluoroquinolones including ciprofloxacin. Amoxicillin-clavulanate was chosen in the study in the hopes of finding an effective fluoroquinolone-sparing antibiotic for the treatment of uncomplicated cystitis. Unfortunately, amoxicillin-clavulanate is not a reliable option and alternatives will need to be found (*JAMA.* 2005;293:949-955).

AD Therapy and Cognitive Function

Men with prostate cancer who note worsening cognitive function in the early stages of androgen deprivation (AD) therapy should consider that the change is due to the treatment not the disease, according to new study published online in the "Early View" section of *Cancer*. Researchers from Finland followed 23 men undergoing AD for prostate cancer. Thirty-one cognitive tests were performed at baseline, 6 months, and 12 months into therapy. Testosterone and estradiol locals were followed throughout treatment. Visual memory of figures in recognition speed of numbers were significantly impaired at 6 months. Surprisingly, some men with the lowest change in estradiol levels had an improvement in verbal fluency and 12 months. The author suggests that cognition may be adversely affected during androgen deprivation (*Cancer*-published online 2/16/05).

LDL Lowering in CHD Patients

An LDL target in the 70s for CAD patients may become the standard, as evidence continues to mount for the benefit of intensive cholesterol lowering. The latest study from the "Treating to New Targets" or TNT investigators looked at 10,000 patients with stable coronary disease and LDL levels less than 130. Patients were randomized to atorvastatin 10 mg/day (low dose) or 80mg/day (high dose) and were followed for an average of 4 years. Mean LDL cholesterol was lowered to 101 mg/dL in the low-dose group and to 77 mg/dL in the high-dose group. Persistent elevations in liver enzymes was more common in the high-dose group (0.2% low dose, 1.2 % high dose [$P <$ .001]). The study end points were cardiovascular events including death from CHD, nonfatal MI, resuscitation after cardiac arrest, or stroke (fatal or nonfatal). A primary event occurred in 548 patients in the low-dose group (10.9%) and 434 patients in the high-dose group (8.7%) for a 2.2% absolute rate reduction (HR, 0.78; 95% CI, 0.69-0.89; $P <$ .001). There was a higher death rate from noncardiovascular causes in the high-dose treatment group, and no difference in overall mortality. There were no trends in the noncardiovascular deaths, specifically no higher rate of cancer or violent deaths. The authors conclude that aggressive LDL lowering is warranted in CHD patients (*N Engl J Med*-published online March 2005). An accompanying editorial suggests more caution, stating, "Patients and their physicians will need to carefully weigh the benefits or a reduction in the risk of cardiovascular events. . . against the uncertainty of an increase in the risk of death from noncardiovascular causes" (*N Engl J Med*-published online March 2005).

FDA Actions

The FDA and federal marshals from the Department of Justice have seized Paxil CR and Avandamet tablets manufactured by GlazxoSmithKline at its plants in Knoxville, TN, and Puerto Rico. The FDA stated that the seizures were prompted by violations of manufacturing standards that resulted in the production of poor quality drug products, including tablets that could split apart and tablets that had inaccurate doses of the active ingredient.

In late February, the FDA issued a public health advisory regarding nataluzimab (Tysabri), Biogen's recently approved drug for the treatment of relapsing forms of multiple sclerosis. Marketing of the drug has been suspended while the agency and the manufacturer evaluate 2 cases of progressive multifocal leukoencephalopathy in MS patients who were using the drug, one of which resulted in death. Nataluzimab received accelerated approval in November 2004, and 8000 patients have received the drug, including 3000 who received it during clinical trials. ■