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Outcome of Preventive Surgery and Screening for Breast and Ovarian Cancer in BRCA Mutation Carriers

ABSTRACT & COMMENTARY

To prospectively determine the effect of genetic counseling and testing on risk-reduction strategies and cancer incidence in a cohort of individuals at hereditary risk for breast and ovarian cancer, Scheuer and colleagues identified 251 individuals with BRCA mutations at a single comprehensive cancer center from 1995 through 2000. Uniform recommendations regarding screening and preventive surgery were provided in the context of genetic counseling. Patients were followed for a mean of 24.8 months (range, 1.6-66.0 months) using standardized questionnaires, chart reviews, and contact with primary physicians. Frequency of cancer surveillance by physical examinations and imaging studies increased after genetic counseling and testing. Twenty-one breast, ovarian, primary peritoneal, or fallopian tube cancers were detected after receipt of genetic test results. Among 29 individuals choosing risk-reducing mastectomy after testing, 2 were found to have occult intraductal breast cancers. Among 90 individuals who underwent risk-reducing salpingo-oophorectomy, 1 early-stage ovarian neoplasm and 1 early-stage fallopian tube neoplasm were found. Radiographic or tumor marker-based screening detected 6 breast cancers, 5 of which were stage 0/I, on early-stage primary peritoneal cancer, and 3 stage I or II ovarian cancers. Six additional breast cancers were detected by physical examination between radiographic screening intervals; 4 of these 6 tumors were stage I. No stage III or stage IV malignancies were detected after genetic testing. Scheuer et al concluded that this study provides prospective evidence that genetic counseling and testing increased surveillance and led to risk-reducing operations, which resulted in diagnosis of early-stage tumors in patients with BRCA1 and BRCA2 mutations (Scheuer L, et al. *J Clin Oncol*. 2002; 20:1260-1268).

■ COMMENT BY DAVID M. GERSHENSON, MD

With the discovery of the BRCA gene mutations in the 1990s and

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INSIDE

the almost simultaneous recognition of women at high risk for the development of breast, ovarian, and related gynecologic cancers, several large centers established high-risk screening programs for risk assessment, prevention, early detection, and surveillance. The group at Memorial Sloan-Kettering Cancer Center has been in the forefront of this paradigm shift. This study reports the experience of these investigators with women with BRCA mutations. Based on identification of these BRCA1 or BRCA2 mutations, women underwent more intense surveillance or prophylactic surgery. Scheuer et al have detailed a number of cancers diagnosed at a relatively early stage. The implication of this study is that women who may be at high risk of developing breast, ovarian, or related cancers (fallopian tube, primary peritoneal) based on family history or personal history of breast cancer should consider enrolling in a comprehensive screening program such as this one rather than simply requesting periodic ovarian screening or genetic testing from their physician. Such a program provides comprehensive risk assessment, genetic counseling, and psychosocial support. In addition, we will continue to gain additional knowledge about optimal approaches through the accrual of large numbers of women studied in a systematic fashion. Stay tuned for several other similar reports from major centers. ■

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Evaluation of a Consumer-Oriented Internet Health Care Report Card

ABSTRACT & COMMENTARY

Synopsis: *Consumer-oriented rating systems of hospitals may successfully categorize groups of hospitals but do not accurately reflect differences among individual hospitals.*

Source: Krumholtz H, et al. *JAMA*. 2002;287:1277-1287; 1323-1325.

MANY DIFFERENT ORGANIZATIONS, INCLUDING FOR profit web-based companies, have attempted to develop "report cards" that compare the "quality of care" of hospitals. Little has previously been published about the accuracy of such ratings. Krumholtz and associates attempt to examine closely one rating system (HealthGrades.com) for one disease (acute myocardial infarction [AMI]). HealthGrades.com places hospitals that deal with a specific disease—in this case AMI—into various rating groups. At the time this article was prepared, the company used a 5-star rating system that has since been modified. Five-star hospitals were reported to be the best and 1 star the worse. The company uses publicly available Medicare administrative data and a proprietary (never publicly revealed) algorithm to arrive at its ratings. The company determined which hospital fit in which category by comparing the "predicted mortality rate" to the "observed mortality rate" using demographic, clinical, and procedural information. The 1-star and 5-star ratings were assigned to the "worst" and "best" hospitals.

For comparison, Krumholtz et al used the data that had been collected by the Cooperative Cardiovascular Project (CCP). This was a federally funded project that abstracted nationwide data from hospital charts for more than 200,000 hospitalizations for AMI. Rather than using only mortality data, Krumholtz et al used CCP data on 6 process-of-care measures. These included the use of reperfusion therapy, early aspirin use, early beta-blocker use, aspirin at discharge, beta-blockers at dis-

charge, and ACE inhibitors at discharge.

Krumholtz et al detailed the reasons for excluding a large percentage of the CCP cases that had been abstracted at nearly 1500 hospitals. They also described their analyses in sufficient detail.

In general, Krumholtz et al confirmed that these CCP data correlated, in a general way, with the 5-star ratings of HealthGrades.com. The only differences in process between the highest- and lowest-rated hospitals were for the use of aspirin and beta-blockers at the time of admission and discharge. Likewise, there was lower in-hospital mortality at 5-star hospitals when compared to 1-star hospitals both in adjusted and unadjusted mortality rates.

While Krumholtz et al confirmed general differences in the hospital groupings, they also reported that most of the hospitals in all 5 groups performed exactly the same. Indeed, when 1-star and 5-star hospitals were compared ". . . in 92.3% of comparisons, 1-star hospitals had a risk standardized mortality rate that was not statistically different than that of a 5-star hospital . . ." Nonetheless, the 30 day crude-mortality rate for 1-star hospitals was 23% and 15.4% for 5-star hospitals.

Krumholtz et al carefully note the strengths and weaknesses of their analyses. They carefully point out that it is difficult to develop rating systems, and that all are subject to error as they only have a given set of data to review. Overall, they remain somewhat negative concerning the public value of rating systems because "the public . . . often becomes focused on identifying single 'winners and losers' rather than using these data to inform quality improvement efforts."

In an entertaining accompanying editorial, Dr. Naylor first provides a fictitious comic introduction then briefly discusses the physician's changing role in discussing disease and treatment with patients, reprises the findings of the Krumholtz et al article, and finally (and in my opinion most importantly) discusses the fact that confidential (nonpublic) ratings of doctors and hospitals have resulted in some improvement in care.

■ COMMENT BY KENNETH L. NOLLER, MD

I suspect that almost all of our readers have worked at a hospital that has either voluntarily or reluctantly participated in some type of quality assessment survey. Such surveys generally sound like a good idea to those who have not participated in them.

I have been involved with many of these surveys over the past dozen years or so and have continuously worried about the accuracy. I have seen the results of hospital ratings based on patient comments that have become published widely, and those hospitals scoring poorly suffering as a result. You might wonder, why am I worried about the results of a poor patient satisfaction becoming known? The reason is that I have observed manipulation of patients in an attempt to improve ratings. Some hospitals actually hire individuals to circulate among in-patients and remind them how good their care is, and ask them to note that "fact" when they receive their patient survey in the mail. That alone would invalidate the results.

However, it gets even worse. In the past few years I have seen hospitals, hospital administrators, and department chairs suffer because their hospital (for a specific service or a portion of a service) received a "statistically significant lower rating" than another hospital. On one occasion, this difference was the result of 21 patients at hospital A rating the service as excellent and only 20 doing so at hospital B. Hospital B was listed in the local paper as being "significantly" lower rated.

I strongly recommend that you read this *JAMA* article and the accompanying editorial. While the disease chosen for the study is myocardial infarction, it could just as easily have been some OB/GYN malady. The importance of the article is that it carefully examines the problems with hospital rating systems. The accompanying editorial points out that it is not at all certain that such rating systems make any particular difference in the quality of care received by patients, and suggests alternate methods that have been shown to be (more) useful. Unlike some articles that deal with complicated analyses, this one happens to be quite easy to read and understand. ■

OTC Antifungal Drug Misuse Associated With Patient-Diagnosed Vulvovaginal Candidiasis

ABSTRACT & COMMENTARY

Synopsis: *Slightly more than one half of women who purchased antifungal vaginal medications in this survey had demonstrable vulvovaginal candidiasis.*

Source: Ferris D, et al. *Obstet Gynecol*. 2002;99: 419-425.

FERRIS AND ASSOCIATES ATTEMPTED TO ESTIMATE THE proportion of women who purchased antifungal over-the-counter (OTC) medications who actually had

the disease. They also examined whether a previous history of candidiasis or reading the OTC package label improved a woman's diagnostic accuracy.

Ferris et al collected cases from 5 urban areas. Women were required to be 18 years of age or older, were in the process of purchasing an antifungal medication, and presented for examination prior to using the purchased material. The women were recruited by pharmacists and other employees of pharmacy and grocery stores in the study cities. Despite having a metropolitan female population of several million, only 104 women were initially enrolled in the study during the 4-month study window. Of these, 9 were excluded.

All of the women who agreed to participate in the study were examined within 24 hours of their product purchase. All women had microscopic evaluation of their vaginal secretions. Multiple cultures were obtained, as well as a Gram stain of the vaginal secretion. Cultures for chlamydia and gonorrhea were performed.

Only one third of the women had vulvovaginal candidiasis alone, but a total of 53.5% had candidiasis with or without bacterial vaginosis or trichomonas. Overall, only 13 of the 95 women were found to be completely normal. (Of interest, Ferris et al do not comment on their interpretation of the reason these women were having symptoms.)

Based on these results, Ferris et al conclude that nearly half the women in their sample were wasting their personal health care dollars by purchasing OTC antifungal agents. They also suggest the primary beneficiaries of the OTC availability of these medications are the pharmaceutical companies. However, they do suggest that because nearly one half of the women did have a yeast infection and would presumably have been cured of that condition with the OTC medication without a physician examination, the overall health care industry expense might be less than when these medications were only available by prescription.

■ COMMENT BY KENNETH L. NOLLER, MD

This article represents another in an ever-lengthening series that has shown that many women who purchase OTC antifungal medications for the treatment of yeast vulvovaginitis do not, in fact, have that disease. I really don't think that fact should surprise anyone, as even clinicians have been known to misdiagnose a vulvovaginal candidiasis with some frequency.

The interesting part of this article was Ferris et al's examination of the usefulness of the "restrictions" the FDA placed on the use of these medications. These were that the medications should only be used in women who had previously had a clinician-confirmed case of candidiavaginitis, and that they have read the product package. Ferris et al found that women who actually had vulvovaginitis were no more or less likely to have fit these 2 restrictions than women who did not have the disease. Clearly the FDA has not provided useful guidance in this case.

While Ferris et al largely avoided it, I am somewhat tired of having clinicians whine about the fact that these drugs are available OTC since some women who take them do not actually have yeast vulvovaginitis. Virtually all OTC medications are used inaccurately on some occasions. For example, I have no doubt that some individuals who purchase aspirin because they have a headache actually have a brain tumor for which the aspirin will not provide relief. Does that mean aspirin should be taken off the market?

My only concern with these OTC antifungal agents is that some women use them repeatedly because they are not "cured." I have frequently seen women in the office that have vulvar injuries due to repeated use. I would truly like to see the FDA require that each of these packages state, in bold-face type, that they should not be reused if symptoms do not disappear or recur within a short period of time. ■

Oral Contraceptives and Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Oral contraceptives protect against ovarian cancer, but it is not clear whether specific progestins are more effective than others.*

Source: Schildkraut JM, et al. *J Natl Cancer Inst.* 2002;94:32-38.

SCHILDKRAUT AND COLLEAGUES FROM THE DUKE University Medical Center conducted a case-control study examining the association between the risk of ovarian epithelial cancer and the specific estrogen and progestin components of oral contraceptives. The 390 cases and 2865 controls were obtained from the Cancer and Steroid Hormone Study (CASH). The cases in this multicenter study were diagnosed in a 2-year period, from December 1980 to December 1982. The results confirmed older studies finding that combined estrogen-progestin oral contraceptives (OCs) protect against ovarian cancer, but Schildkraut et al further concluded that formulations with a high-progestin potency produce a greater

reduction in risk compared with low-progestin potency products. The results were expressed by using high-progestin potency as the referent; thus low-progestin potency products had a 2.2 odds ratio (CI = 1.3-3.9), a greater risk of ovarian cancer (based on 22 cases with high potency, and 82 cases with low potency). Analysis by duration of use indicated increasing protection with increasing duration of use, with a slightly better effect associated with high-potency products. Schildkraut et al concluded that OCs with a high potency progestin provide greater protection against ovarian cancer, and suggest that this is due to a direct biologic effect other than inhibition of ovulation.

■ **COMMENT BY LEON SPEROFF, MD**

Schildkraut et al were partly motivated to perform this study because they had previously published the results of a study in monkeys that the progestin component of OCs produces a direct apoptotic effect on the ovarian epithelium.[1] They were pleased with the results of their case-control study; therefore, because they supported their contention that progestin exerts a beneficial effect beyond inhibition of ovulation. However, the results are not so clear cut.

The conclusion depends upon the validity of assigning progestin potency to the different formulations. It is difficult to make this exercise clinically meaningful because potency varies depending upon the target organ and end point being studied. The 2 methods chosen were "delay of menses" and "subnuclear vacuolization in human endometrium." Differences in these assays may have little meaning in a different target tissue—in this case the ovary. Furthermore, animal responses differ compared with human responses. Finally, potency differences in various progestins have been accounted for clinically by appropriate adjustments in the administered doses.

Schildkraut et al acknowledge that there exists in the literature another case-control study of comparable size (actually twice as many cases) and design with a different conclusion (these are the 2 best studies on the subject). Ness and colleagues reported in 2000 that they could not detect a difference in the reduced risk of ovarian cancer comparing women who used higher dose pills before 1972 with women who used lower dose pills after 1980.[2] In this study, both high progestin products and low progestin products had the same 50% reduction in ovarian cancer risk, and the case numbers were 49 and 140, respectively (compared with 22 and 82 in the current report). Both studies used the same methods to assess potency and the same technique to ascertain which products were used.

Schildkraut et al in this current report state in their discussion that "newer formulations have had lower potencies and, therefore, are likely to have a reduced effect on the risk of ovarian cancer." I strongly believe it is inappropriate to make such an important clinical conclusion based on these data. There is no way to know if the results of this most recent study are real or reflect the case numbers and/or the categorization and labeling of products into high and low potency. Furthermore, a case-control study of even larger size and similar design fails to reach the same conclusion. I'm sure the authors were delighted to have support for the biologic effects of progestins demonstrated in their monkey study, and this does lend biologic plausibility to their case-control results, but these results are not sufficient to influence clinicians as to which OCs should be prescribed.

The literature on OCs and the risk of ovarian cancer supports the following important conclusions:

- OCs reduce the risk of ovarian epithelial cancer, about 40% overall;
- The degree of reduction increases with increasing duration of use;
- The protective effect is maintained for as long as 30 years after discontinuing use;
- The protective effect is independent of age at initiation, young or old;
- The protective effect is independent of the dose of estrogen. ■

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1. Rodriguez GC, et al. *J Soc Gynecol Investig*. 1998;5: 271-276.
2. Ness RB, et al. *Am J Epidemiol*. 2000;152:233-241.

Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era

ABSTRACT & COMMENTARY

Synopsis: *During the platinum era, maximal cytoreductive surgery was one of the most powerful determinants of cohort survival among patients with advanced ovarian cancer.*

Source: Bristow R, et al. *J Clin Oncol*. 2002;20: 1248-1259.

Bristow and associates identified 28 cohorts of patients with stage III or IV ovarian cancer (6885 patients) from articles in MEDLINE (1989-

1998). Linear regression models, with weighted correlation calculations, were used to assess the effects on log median survival time of the proportion of each cohort undergoing maximal cytoreduction, dose-intensity of the platinum compound administered, proportion of patients with stage IV disease, median age, and year of publication. There was a statistically significant positive correlation between percent maximal cytoreduction and log median survival time, and this correlation remained significant after controlling for all other variables ($P < .001$). Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. When actuarial survival was estimated, cohorts with < 25% maximal cytoreduction had a mean weighted median survival time of 22.7 months, whereas cohorts with more than 75% maximal cytoreduction had a mean weighted median survival time of 33.9 months—an increase of 50%. The relationship between platinum dose-intensity and log median survival time was not statistically significant. Bristow et al concluded that during the platinum era, maximal cytoreduction was one of the most powerful determinants of cohort survival among patients with stage III or IV ovarian cancer. Consistent referral of patients with apparent advanced ovarian cancer to expert centers for primary surgery may be the best means currently available for improving overall survival.

■ **COMMENT BY DAVID M. GERSHENSON, MD**

Since the reports of seminal studies of primary cytoreductive surgery for advanced epithelial ovarian cancer appeared in the 1970s, this procedure has been the cornerstone of treatment for this condition. These studies revealed that patients with minimal residual disease (< 1-2 cm) at the completion of primary surgery had a better survival than those with bulky residual disease. However, because there are no randomized trials comparing primary surgery with no surgery, the precise value of such an intervention has remained in question. In other words, it has been difficult, if not impossible, to distinguish the effects of the biology of the ovarian cancer from the influence of the surgical intervention. Although the present meta-analysis does not resolve this issue, it does significantly strengthen the argument that primary cytoreduction does play a major role in the overall therapeutic approach to advanced ovarian cancer. In fact, in the multivariate analysis, the percent maximal cytoreductive surgery was the most powerful independent factor associated with survival. Of course, major limitations of any meta-analysis, as pointed out by Bristow et al, include the potential for selection bias and the imprecision of data measurement. The major implication for a study such as this is the importance of maximizing a woman's opportunity for optimal cytoreduction. Several studies have detailed the fact that women with suspected ovarian cancer should seek consultation with a gynecologic oncologist. This recommendation is based on observations that such experts are more likely to accomplish optimal cytoreductive surgery with minimal residual disease than nonexperts, thereby improving the probability of survival. ■

Special Feature

Current Management of Rh and Kell Sensitization

By John C. Hobbins, MD

SINCE THE ADVENT OF ANTI D IMMUNE GLOBULIN, THE incidence of Rh sensitization and, consequently, erythroblastosis fetalis has plummeted—but not to zero. We generally are following 2 or 3 patients a month who are either Kell or Rh sensitized as a result of insufficient or ill-timed delivery of anti-immune globulin or mismatched transfusions.

Some recent developments have allowed a kinder, less invasive approach to management of these patients. The "old" way, unfortunately still used by some clinicians in the United States, was to perform antibody testing monthly in all sensitized patients. If the antibody titer rose above 1:16, an amniocentesis was used to assess the optical density difference (DOD) in amniotic fluid. Since indirect bilirubin was absorbed at 450 mm, the difference between the actual absorbance and that expected (if no bilirubin were there) gave the clinician an indirect idea of how much hemoglobin was being broken down by maternal antibodies. The "DOD 450" was then plotted into a 3-zone curve according to gestational age, which was originally developed 4 decades ago by Liley and later modified by others such as Frigoletto and Queenan.

This type of assessment was reasonably good at predicting the unaffected or mildly affected fetus if the DOD 450 fell into Zone I or lower Zone II, but it was an inconsistent predictor of severe disease because of the inherently high false-positive rate. However, the biggest problem came from the invasive aspect of this approach. Many patients had amniocenteses every 2 weeks and, not infrequently, completely unnecessary cordocentesis based on an erroneously high DOD 450. Amniocentesis and cordocentesis have risks of their own that, although

low for fetal death with amniocentesis, are not inconsequential when considering infection or need for emergency cesarean section—something that we have had to do on occasion for nonreassuring heart tones after an amniocentesis or cordocentesis in the third trimester. Also, when a needle strays near or into the placenta, the potential for worsening sensitization exists throughout pouring of antibody when fetal cells enter the maternal circulation.

Mari and colleagues first reported a relationship between peak velocity in the fetal middle cerebral artery (MCA) and the severity of fetal anemia.[1] When the fetus is anemic, the oxygen delivery is diminished to most tissues, simply because there are fewer working red blood cells. The fetus then attempts to protect his or her brain by giving special circulatory attention to the cortex. Anemic blood has a low viscosity and, therefore, enters the middle cerebral arteries at high-peak velocities. With carefully angle-corrected Doppler measurements, the peak velocity can be accurately quantified.

Mari et al constructed a nomogram based on peak velocities at different gestational ages. The higher the peak velocities above 1.5 MoM, the greater the chance of severe fetal anemia. Levels below 1.5 MoM are indicative of a fetus that needs no special attention at the time of the test.

Large prospective studies by Mari et al, and now others, have suggested that the false-negative rate of a reassuring peak velocity (below 1.5 MoM) is extremely low (< 1%), and the false-positive rate of values above 1.5 MoM is about 12%. We have used this technique for the last 5 years in conjunction with other ultrasound signs of fetal anemia (spleen size, live size, pre-ascites, pericardial effusion, echogenic bowel) and have yet to encounter evidence of severe fetal anemia in the face of a reassuring MCA peak velocity. This approach has almost completely eliminated the need for invasive testing since in the overwhelming majority of cases the MCA peak velocity is reassuring.

The following represents our current approach to the Rh sensitized or Kell patient:

- If the patient is Rh negative or Kell negative and has antibodies on first visit, we will encourage the father of the baby to have zygosity testing;
- If he is negative for the antigens in question, no further testing is necessary (unless there is a question of paternity);
- If he is heterozygous for the Rh or Kell factor, then in the second trimester we might suggest testing the Rh or Kell status of the fetus through amniocentesis;
- If titers are consistently low, however, the amnio might be waived or postponed until there is an elevation above 1:16, or an amniocentesis planned for another reason (AMA);
- If the fetus is Rh negative or Kell negative—a 50% likelihood when the father is heterozygous—then no further testing is needed;
- If the father is homozygous or the fetus is found to be positive by amniocentesis, then Dopplers of the MCA are undertaken every 2 weeks.

The good news is that invasive procedures are rarely required. However, if the peak velocity is above 1.5 MoM and the pregnancy is less than 34 weeks, we will then book the patient for a cordocentesis and possible intra-uterine transfusion. Subsequent procedures will be predicated upon the gestational age, the hematocrit of the fetus at the end of the transfusion, and weekly MCA Doppler findings. (The peak velocities will drop dramatically immediately after an intra-uterine transfusion.)

This protocol represents a safe and effective way to save potentially risky procedures for only those few patients who really need them. ■

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2. Mari G, et al. *N Engl J Med*. 2000;342(1):9-14.

CME Questions

16. Mutations of which genes are associated with hereditary breast and ovarian cancers?

a. p53 and Retinoblastoma
b. p53 and HER-2/neu
c. BRCA1 and BRCA2
d. BRCA1 and p53
e. BRCA1 and HER-2/neu

17. Based on the article by Krumholtz et al, which of the following statements is most accurate?

a. Rating hospitals through the use of Medicare data is highly accurate.
b. For-profit hospital ratings systems on the web correctly identify the "best" and "worst" hospitals.
c. The risk of death from myocardial infarction in the first 30 days was not significantly different between 5-star and 1-star hospitals.
d. Grouping of hospitals based on some "quality" measure might be statistically accurate, but does not predict important differences between any 2 hospitals.

18. The following statements are true regarding the association between OCs and the risk of ovarian cancer *except*:

a. All combination estrogen-progestin OCs protect against the risk of ovarian cancer.
b. It is not certain whether older high-dose pills are more or less effective compared with modern low-dose pills.

c. Older women who use OCs are more protected than younger women.
d. The mechanism of protection is probably more complicated than just inhibition of ovulation.

19. Based on the article by Ferris et al, in their sample approximately what proportion of patients who purchased antifungal vulvovaginal medications did not have vulvovaginal candidiasis?
a. 1 in 10
b. 1 in 3
c. 1 in 2
d. 3 in 4

20. The principal prognostic factor that is associated with the success of primary cytoreductive surgery for advanced stage epithelial ovarian cancer is:
a. residual disease.
b. histologic grade.
c. histologic type.
d. patient age.
e. presence of ascites.

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PHARMACOLOGY WATCH

FDA: No Approval for Pleconaril; Side Effects Cited

The world will have to wait a while longer for a cure for the common cold. In mid March, the FDA's Antiviral Drugs Advisory Committee voted to not endorse the approval of pleconaril, ViroPharma and Adventis' antiviral drug for inhibiting picornaviruses, the most common cause of the common cold. The drug has been available on an open-label basis since 1996 to treat severe infections caused by picornaviruses. But studies have shown that the effect on the common cold is modest, shortening the duration of symptoms only 0.5 to 1.5 days. More importantly, the drug has been shown to have significant side effects, including increase menstrual bleeding and the drug interactions with some asthma medications. Finally, the committee was also concerned about the selection of resistant viruses with overuse of the drug. ViroPharma may continue research with the drug to establish a safety profile, and try resubmitting in the future.

Statins Reduce Fracture Risk in Elderly

A new study shows that statins are associated with a reduction in fracture risk in older women, even though the drugs do not seem to increase bone mineral density (BMD). Researchers in Australia look at the history of statin use in 1573 women with a history of fractures and 800 matched women without fracture with an average age of 70 years old. After controlling for medication use and lifestyle factors, statin use resulted in odds ratio for fracture of 0.40. Even after adjusting for BMD at the femoral neck, spine, and whole body, the odds ratios were essentially unchanged. The reason for these findings is unclear, but the researchers suggest that statins may have an effect on bone architecture or may reduce the rate of fracture by some other, yet unknown, mechanism (*Arch Intern Med.* 2002;162:537-540).

Levofloxacin Resistance Shown in Study

Levofloxacin is quickly becoming one of the most widely used antibiotics in the country for the treatment of community-acquired pneumonia. Almost predictably, Canadian researchers have recently identified 4 adult patients who failed treatment with levofloxacin and eventually grew levofloxacin-resistant *Streptococcus pneumoniae* from sputum or blood cultures (*N Engl J Med.* 2002;346:722, 747-750). Pneumococcal resistance has also become a serious problem in children as well. Surveillance of pneumococcal isolates from children between 1993 and 1999 showed a marked increase in resistance to several antibiotics over those 6 years. Penicillin resistance increased from 4% to 15% while resistance to ceftriaxone increased from 0.5% to 2%. One-third of children had received antibiotic in the 30 days prior to diagnoses with resistant pneumococcal disease.

Claritin Could Become OTC

Loratadine (Claritin) may be available over-the-counter (OTC) before the end of the year. In a dramatic shift from the company's previous stance, Schering-Plough has asked the FDA for permission to market all strengths of loratadine

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as over-the-counter products. Less than 1 year ago, the FDA independently considered moving loratadine, as well as 2 other nonsedating antihistamines, to OTC status, a move that Schering-Plough vigorously opposed. However, the drug now faces an impending patent expiration in December. Claritin generated $3.2 billion in sales for Schering-Plough last year, which represented about a third of the company's total sales. The company, in hopes of recovering much of that lost revenue, has also introduced desloratadine, the active metabolite of loratadine to great fanfare under the trade name Clarinex. If desloratadine is a winner, the company hopes to control both the prescription market with its new product, and the OTC market with loratadine. Meanwhile, generic houses are lining up to produce a generic version of loratadine, which could be available as early as December 2002.

Ramipril Might Have Additional Benefits

The ACE inhibitor ramipril may have benefits beyond blood pressure lowering in patients who are at risk for stroke. A review of more than 9000 patients in the Heart Outcomes Prevention Evaluation (HOPE) trial revealed that patients treated with ramipril were 32% less likely to experience a stroke than those who received placebo. Patients in the trial were all at high risk for cerebrovascular disease, having pre-existing cardiovascular disease or diabetes plus other risk factors. Patients were randomized to either placebo or ramipril 10 mg per day, after a run-in period of several weeks, and they were followed for 4.5 years. Not only was the rate of stroke reduced by one third, but also ramipril resulted in a decreased risk of fatal stroke of nearly two thirds (61%). Curiously, patients in the ramipril group showed only modest blood pressure lowering (3.8 mm Hg systolic and 2.8 mm Hg diastolic), and the authors and others conjecture that the protective effective ramipril may go beyond its blood pressure lowering properties. The authors also suggest that this may be a class effect of ACE inhibitors. An accompanying editorial conjectures that ACE inhibitors may decrease oxidative stress and decrease proliferative and inflammatory responses in atherosclerotic plaques. They also suggest that the effect of ACE inhibitors is additive to that of aspirin in preventing stroke (*BMJ*. 2002;324:699-702, 687-688).

Losartan More Effective Than Atenolol

In a head-to-head study of losartan vs. atenolol, the angiotensin II receptor blocker losartan was shown to be more effective at reducing cardiovascular mortality and morbidity than the beta-blocker atenolol. In a multinational trial of more than 9000 patients aged 55-80 with hypertension and left ventricular hypertrophy (LVH), patients were randomized to losartan or atenolol-based antihypertensive treatments for 4 years. The blood pressure lowering effect of both medications was similar, approximately 30 mm HG drop in systolic pressure and a 16.5 mm Hg drop in diastolic pressure for both drugs. The primary composite end point (cardiovascular death, myocardial infarction, or stroke) was lower in the losartan group (23.8 per 1000) compared with the atenolol group (27.9 per 1000). The death rate and rate of nonfatal or fatal stroke was lower with losartan, while the rate of myocardial infarction was slightly higher with losartan although not statistically significant. Interestingly, the rate of new onset diabetes was 25% lower in patients taking losartan. The authors point out that this study does not condemn beta-blockers, with studies showing the drugs reduce cardiovascular event by 45% vs. placebo. They also point out that the beneficial effects of losartan may be incremental and additive to the benefits of beta-blockers in preventing cardiovascular disease, and that the drugs may, and perhaps should, be used together in these patients. However, the study also showed that losartan was better tolerated than atenolol (*Lancet*. 2002;359:995-1003). A related study from the same journal compared losartan to atenolol in patients with hypertension and diabetes. Nearly 1200 patients with diabetes, hypertension, and LVH were randomized to losartan or atenolol-based treatment regimens. Again, a pressure reduction was similar in both groups. The primary end points (cardiovascular disease, stroke, or myocardial infarction) occurred in 103/586-losartan group vs. 139/609 atenolol group (relative risk, 0.76). All-cause mortality was significantly lower in the losartan group, as was cardiovascular mortality (relative risk, 0.63 and 0.61, respectively). The authors of the study conclude that losartan is more effective than atenolol in reducing cardiovascular morbidity and mortality in patients with hypertension and diabetes with LVH. As in the previous study, the authors also conclude that the benefits of losartan seem to be more than just an antihypertensive effect (*Lancet*. 2002;359:1004-1010). ■