

REPORTS OF COUNCIL ON SCIENTIFIC AFFAIRS

The following reports, 1-6, were presented by Roy D. Altman, MD, Chair:

1. UNIVERSAL ROUTINE SCREENING OF PREGNANT WOMEN FOR HIV INFECTION (RESOLUTION 511, I-00)

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTION 511 (I-00) AND REMAINDER OF REPORT FILED

Resolution 511 (I-00), introduced by the International College of Surgeons - US Section at the 2000 Interim Meeting and referred to the Board of Trustees, asks:

That our American Medical Association (AMA) endorse routine prenatal HIV screening; and

That our AMA shall develop a legislative package for passage of this concept nationally.

Testimony at the Reference Committee overwhelmingly supported the implementation of routine prenatal HIV screening for pregnant women, with the final decision for HIV testing lying with the woman. However, there also was significant discussion as to whether mandatory prenatal HIV screening of pregnant women as supported by current AMA policy is appropriate. Thus, the resolution was referred to the Board of Trustees, resulting in this Council on Scientific Affairs report.

DATA SOURCES

- Literature searches were conducted in the MEDLINE database for articles published between 1996 to 2001 using the search terms "AIDS" or "HIV" in combination with "perinatal transmission" or "prenatal screening" or "pregnancy," yielding a combined total of 1401 references. One hundred sixty-two English-language references, from 1998 to 2001, were examined further. Additional references were culled from the bibliographies of these references.
- Lexis/Nexis news databases were searched for current developments using the search term "HIV and perinatal transmission."
- The World Wide Web was searched with several different search engines for information using the search words "HIV" or "AIDS" in combination with "perinatal transmission" or "prenatal screening."

EXISTING AMA POLICY

Existing AMA policy on the perinatal transmission of HIV is provided in Appendix A.

PERINATAL TRANSMISSION OF HIV IN THE UNITED STATES - AN UPDATE

Background

Perinatal transmission (also known as vertical transmission) of HIV is the most common cause of HIV infection in infants and children in the United States and is responsible for slightly more than 90% of pediatric AIDS cases and almost all new HIV infections in preadolescent children. As of December 2000, adult women account for about 30% of US cases of HIV infection and 25% of AIDS cases, and 78% of HIV-infected women are members of a racial or ethnic minority. In 2000, young women of childbearing age (aged 20 to 39 years) comprised 68% of AIDS cases in women. This prevalence data suggest, and other studies of incidence of HIV in women show, that the rate of HIV infection in young women of childbearing age continues to increase in the United States. The HIV/AIDS epidemic in children strongly paralleled the growing epidemic in women until 1994, when antiretroviral prophylaxis was shown to reduce perinatal HIV transmission.

Reports on the worldwide frequency of transmission of HIV from mother to child vary greatly, ranging from 11% to more than 40% of children born to HIV-infected mothers, with transmission rates approximately doubled in breast-fed compared to formula-fed children. These figures are derived from polymerase chain reaction and virus culture studies, as maternal antibodies are present in the newborn at birth and may persist for up to 18 months. In North America, in the absence of breastfeeding and antiretroviral intervention, the most widely quoted figures range from 15% to 25%. Variability in estimated transmission rates is believed to be due to a difference in prevalence of risk factors such as breastfeeding, premature birth, nutritional deficiencies, obstetrical practices, and maternal viral load. Thus, in countries in Africa, the transmission rates can be as high as 40% or more. Some of these factors have only recently been identified and are discussed further below.

In the United States before 1994, it was estimated that 2000 children were born annually with HIV transmitted from their mothers. As of 2000, a total of about 8,700 perinatally HIV-infected children had been born. A disproportionate number (more than 84%) are African American or Hispanic.

In 1994, the landmark Pediatric AIDS Clinical Trial Group (PACTG) Protocol 076 demonstrated that a three-part zidovudine regimen administered to selected women and their newborns reduced perinatal transmission from 25% to 8%. As a result, the United States Public Health Service (USPHS) in 1994 released its first recommendation for the use of zidovudine to reduce perinatal transmission and in 1995 released its revised recommendations for HIV counseling for, and voluntary testing of, pregnant women. These new recommendations moved away from the targeted approach of the original 1985 recommendations on HIV counseling and testing in the prenatal setting--written when very little was known about perinatal HIV transmission--towards a more universal approach. They recommended that "health care providers ensure that all pregnant women are counseled and encouraged to be tested for HIV..." and that the testing should be voluntary and not mandatory.

Because of the rapid implementation of these guidelines and increased prenatal HIV counseling and testing, perinatal HIV transmission rates have decreased dramatically to levels as low as 5% with administration of zidovudine. In 1996, combination therapy with protease inhibitors became available, resulting in increased use of combination antiretroviral therapy during pregnancy. In 1998, the USPHS released its prophylactic treatment guidelines for use of antiretroviral agents (including combination therapy) during pregnancy for maternal health and reduction of perinatal transmission. Such combination therapy led to reported transmission rates as low as 1.5% in 1999. In 1999, it was also demonstrated that one dose of nevirapine given to the mother at labor and delivery and one dose given to the baby could reduce transmission 47% relative to a short regimen of intrapartum/one week neonatal zidovudine alone. Studies on the use of nevirapine and other antiretroviral agents to reduce perinatal transmission are ongoing. Finally, it has been shown that the use of scheduled cesarean section in the presence of zidovudine therapy can reduce the rate of perinatal HIV transmission to as low as 1%.

In May 2001, the USPHS released the latest version of its recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the US (Appendix B provides a summary; the full document is available at: www.hivatis.org/trtgdlns.html#Perinatal). These recommendations are now updated regularly (considered a "living document"), and the latest revision reflects the availability of aggressive combination therapy to maximally suppress viral replication. They further state that while pregnancy may affect decisions of timing and choice of therapy, it is not a reason to defer standard treatment. However, it is stressed that the use of antiretroviral drugs during pregnancy requires unique considerations, and data on short-term effects on the fetus, newborn, and mother are limited and the potential long-term effects on the child and mother are unknown. In addition to considering potential toxicity during pregnancy, the guidelines emphasize that two separate but closely related issues must also be considered. First, the use of antiretrovirals for treatment of HIV infection in the woman, and second, the use of antiretrovirals to reduce the risk of perinatal transmission. Thus, the recommendations for a treatment-experienced HIV-infected pregnant woman may differ from those for a treatment-naïve woman.

The revised recommendations also stress that because of these unknowns, offering antiretroviral treatment to HIV-infected women should be accompanied by a discussion of the known and unknown short- and long-term benefits and risks of such treatment for the women and their infants. *It is highly recommended that health care professionals consult these USPHS recommendations, and/or seek consultation from HIV experts, when treating pregnant HIV-1-infected patients.*

The most recent surveillance data indicate the dramatic effects of the implementation of these guidelines for universal counseling and voluntary HIV testing of pregnant women and the use of zidovudine on the perinatal transmission of HIV in the United States. Besides the obvious decline in rates of perinatal transmission discussed above, the number of estimated pediatric AIDS cases diagnosed each year has declined steadily since 1993. Between the first half of 1994, when the results of PACTG 076 were released, to the end of 1998, a 79% decline in the number of perinatal AIDS cases occurred. This decline coincides with the increased use of zidovudine, which rose from 13% in 1993 to 87% in 1998.

In 2000, only 174 pediatric AIDS cases were reported in the United States, but perinatal transmission remains responsible for 90% of all pediatric AIDS cases. Development of AIDS, however, is a late manifestation of perinatal HIV infection. As perinatal HIV infection is not yet reportable in all states, it is difficult to obtain exact numbers. However, the Centers for Disease Control and Prevention (CDC) currently estimates that, in the United States, no more than 300 infants a year acquire perinatal HIV infection. Thus, current recommendations for universal counseling and voluntary HIV testing of pregnant women and the use of zidovudine in HIV-infected pregnant women have dramatically reduced perinatal HIV transmission, such that it is now possible to consider the elimination of perinatal HIV transmission in this country.

Factors Associated with Perinatal Transmission

Dynamics of Transmission: Understanding the dynamics of perinatal transmission is important to designing and evaluating interventions to prevent such transmission. It is now known that there are three principal periods when perinatal transmission of HIV can occur: during pregnancy (in utero), during labor and delivery (intrapartum), and during breastfeeding (postpartum). In a non-breastfeeding population, it is predicted that about 70% of perinatal transmissions occur at delivery and about 30% of transmissions occur in utero. About 67% of the in utero transmissions are thought to be due to virus transmitted during the last 14 days before delivery.

Infections occurring in utero are most likely the result of transplacental HIV transmission, either through breaks in the placental barrier (eg, development of chorioamnionitis), infection of placental cells leading to fetal infection, or transfer of cell-free virus across the placenta to the fetus (eg, through receptor-mediated endocytosis). Evidence supporting the direct in utero transmission of HIV includes the discovery of HIV in aborted fetuses as early as 8 weeks into gestation, and the isolation of HIV-1 from the peripheral blood of neonates at birth.

However, it is generally believed that intrapartum infection is responsible for the bulk of perinatal HIV transmissions. Intrapartum HIV transmission occurs when infectious fluids from the mother directly contact the fetus during maternal-fetal microtransfusions of blood during uterine contractions; ascending HIV infection through the cervix or vagina; or by the infant swallowing HIV present in maternal genital secretions during passage through the birth canal, with subsequent viral transmission by direct infection of gastrointestinal cells or indirect transfer of cell-free virus to lymphoid cells present in the gastrointestinal mucosa. Studies show that about 50% of HIV-infected infants born to HIV-positive mothers have undetectable virus levels at birth, but during the first week following delivery, HIV becomes detectable. Other studies have demonstrated reduced HIV infection in infants born by cesarean section and increased transmission during prolonged rupture of membranes. These data support the concept of infection of the newborn during labor and delivery.

Breastfeeding: Studies performed in Africa where breastfeeding remains a common practice among HIV-infected mothers as a result of socioeconomic factors reveal that as many as 50% of perinatal transmissions are due to breastfeeding following birth. Not surprisingly, HIV has been isolated from both cellular and cell-free extracts of human milk from HIV-infected women, and rates of infection of the infant are higher when the mother seroconverts during breastfeeding, possibly associated with an increased maternal viral load. Little is known about when the greatest risk for transmission via breastfeeding occurs, but it is believed that the highest risk exists during the first few months of life, and that the risk declines thereafter. An international multi-center meta-analysis identified the risk of transmission after the infant is 4 months of age as 3.2 cases per year per 100 breast-fed infants.

Interestingly, recent data from a study in Kenya indicate that breastfeeding by HIV-1 infected women resulted in a maternal mortality rate that was higher than in HIV-infected women using formula. Additionally, there was an association between maternal death and subsequent infant death. Thus, breastfeeding by HIV-1 infected women might actually result in adverse outcomes for both mother and infant. However, data from a study in South Africa did not find increased mortality in breastfeeding women, so this finding remains controversial and requires further research.

Maternal Viral Load: Many studies have now been published demonstrating the importance of maternal viral load in predicting the risk of perinatal transmission. Two recent studies suggest that in pregnant women and their infants, maternal viral load was the best predictor of the risk, but not the timing, of perinatal transmission of HIV. Elevated maternal viral load at the time of delivery may be particularly associated with increased transmission risk. In women and infants receiving zidovudine therapy, antiretroviral treatment that reduced maternal viral load to less than 500 copies/mm³ eliminated the risk of perinatal transmission while improving the general health of the women. Other reports have indicated cases of perinatal transmission of HIV even when viral load is undetectable, although the incidence is extremely rare. Increasing geometric mean levels of plasma HIV-1 RNA were generally associated with increasing rates of perinatal HIV transmission, with the highest rate of transmission among women whose HIV plasma level was more than 100,000 copies/mm³. Finally, in one study, there was no significant difference in the median levels of HIV RNA in mothers of infants with early infection and mothers of infants with late infection, and there was no relation between the rates of early or late transmission and maternal HIV levels measured throughout pregnancy.

Evidence also shows that the use of antiretroviral therapy can help prevent perinatal transmission of HIV even in women with maternal viral loads less than 1000 copies/mm³. For this reason, antiretroviral treatment is recommended for all pregnant women regardless of their plasma HIV RNA levels.

However, data also show that other factors play a role in perinatal transmission. This is suggested by the fact that some transmission of HIV occurs even when maternal viral levels are extremely low and because there is no upper threshold of viral load whereby transmission always occurs. Data also suggest that pre- and post-exposure prophylaxis of the infant plays an important role in determining the rate of perinatal transmission. Premature birth, low birth weight, and longer duration of membrane rupture (more than four hours before delivery) and obstetrical factors such as the intrapartum use of fetal scalp electrodes or fetal scalp pH sampling have also been associated with increased rates of perinatal HIV transmission.

Mode of Delivery: Studies have been done that consistently show that cesarean delivery before the onset of labor and the rupture of membranes significantly reduces the incidence of perinatal HIV transmission, even in women receiving zidovudine. Metaanalysis and other studies demonstrate an additive protection resulting from the combined use of zidovudine and scheduled cesarean delivery. However, it is unknown whether scheduled cesarean delivery provides any benefit to either the mother or the child if the mother is on potent antiretroviral therapy that has lowered plasma viral loads to undetectable levels. However, there also is no threshold viral load below which no perinatal transmission can be guaranteed. Thus, it remains controversial as to whether HIV-infected women on potent antiretroviral therapy with undetectable viral loads should deliver by scheduled cesarean. It is thought unlikely that scheduled cesarean would confer any further benefit to antiretroviral-treated women with low viral loads, as the perinatal transmission rates in this situation are already very low. As such, the American College of Obstetricians and Gynecologists (ACOG) has decided to use a maternal viral load of 1000 copies/mm³ as the threshold, above which it recommends consideration of scheduled cesarean delivery for prevention of perinatal HIV transmission.

Finally, it is important to consider the additional risks associated with cesarean delivery as compared with vaginal delivery. There are data indicating that the risks associated with scheduled cesarean delivery are similar for HIV-infected women and for non-infected women. However, several case-control studies have implied an increased risk in perioperative complications following cesarean delivery in HIV-infected women. In several cases, increased complications were associated with a decreased CD4 T cell count; however, in a prospective study, increased complications were associated with more severe HIV disease but not necessarily with CD4 cell count. Thus, HIV-infected women with low CD4 cell counts are more prone to complications from scheduled cesarean delivery but also stand to benefit most in terms of prevention of perinatal transmission. Consequently, HIV-infected women should be counseled about these increased risks associated with cesarean delivery.

Current Barriers to Eliminating Perinatal Transmission in the United States

Despite the remarkable success of perinatal transmission intervention programs, some perinatal HIV transmission still occurs in the United States. Thus, some barriers to eliminating perinatal HIV transmission continue to exist, the most important being the lack of timely HIV testing and treatment of pregnant women due to poor or absent prenatal care.

The Institute of Medicine (IOM) has detailed a chain of events leading to an HIV-infected infant. This scheme is duplicated below:

The proportion of women...

- Who are HIV-infected
 - Who become pregnant
 - Who do not seek prenatal care
 - Who are not offered HIV testing
 - Who refuse HIV testing
 - Who are not offered the PACTG 076 regimen
 - Who refuse the PACTG 076 regimen
 - Who do not complete the PACTG 076 regimen
 - Whose child is infected despite treatment

Epidemiology of HIV in Women: Before HIV can be transmitted to the infant, the woman must first become infected with the virus. Unfortunately, the recent epidemiology of HIV in US women is disturbing. As discussed above, a significant percentage of women with HIV infection are of childbearing age. In 2000, 79% of HIV infections in women were in those aged 13 to 39 years, and there were more HIV infections in women aged 13 to 19 years than there were in men. It also appears that most of these women (90%) acquired their infection through heterosexual contact. An overwhelming proportion of these women belong to an ethnic minority. Data on HIV prevalence in out-of-school youth (aged 16 to 21 years) in the Job Corps indicate that HIV prevalence was higher in young women than young men, and higher among young African-American women than any other race or gender category.

Unfortunately, these young women at high risk of HIV infection are also at high risk for unintentional pregnancy. Unintended pregnancies also tend to occur frequently in young women infected with HIV. "Street youth" are particularly vulnerable to unintended pregnancy and are also more likely to contract HIV because of high-risk behaviors. To control perinatal transmission of HIV, HIV prevention programs must target these high-risk youth. These programs should also be coupled with efforts to treat substance abuse and to reduce adolescent pregnancy.

Adequacy of Prenatal Care: HIV-infected women need to be identified early in pregnancy in order for the proper counseling and treatment to occur. Recent data from a national CDC study of HIV-infected women indicate that by 1996 all but an estimated 20% of HIV-infected pregnant women had received a diagnosis before delivery, demonstrating successful, albeit not complete, implementation of the voluntary screening guidelines. Of the women who received prenatal care, a large proportion was treated according to the regimens from PACTG 076.

However, 14% of HIV-infected women received no or minimal prenatal care and another 19% did not initiate prenatal care until the third trimester. Twenty-eight percent of HIV-infected women used illicit drugs during pregnancy and of these, 36% received no prenatal care at all. Of women who received HIV testing at or within 7 days of delivery, 71% had received no prenatal care and 67% had used drugs during their pregnancy.

Among HIV-infected women, those at the greatest risk of receiving no or minimal prenatal care are minority women, those living in urban settings, illicit drug users, women with shorter Medicaid enrollment during pregnancy, and those in whom HIV infection is not diagnosed until after delivery. These women usually do not seek prenatal care for reasons such as fear of criminalization, social disruption, the stigmatization associated with illicit drug use, and a general lack of access to health care.

When a woman receives prenatal care, it is also important that she receive adequate counseling about HIV infection and the importance of testing for HIV. Surveys of health care providers indicate that they are likely to offer HIV testing only to women they consider to be at risk for HIV infection, although providers in general agree that all pregnant women should be offered HIV testing. Barriers reported by health care providers include a lack of provider time, the need for counseling and record keeping, and general embarrassment about discussing the issue with patients.

The new recommendation from the IOM (discussed below) and adopted by the USPHS, American Academy of Pediatrics (AAP), and ACOG calls for universal, routine HIV testing of all pregnant women, with patient notification of the right of refusal. For women receiving prenatal care, this new standard should increase the number of HIV-infected women receiving a proper diagnosis. It has been shown that when properly implemented, the

universal offer of HIV testing is not intrusive and is acceptable to pregnant women. However, following diagnosis of HIV infection, it is important to provide adequate counseling about HIV infection and proper advice pertaining to antiretroviral therapy for both treatment of the infection in the woman and reduction of perinatal transmission to the infant. Again, physicians are urged to consult the regularly updated USPHS Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. When antiretroviral therapy is offered to HIV-infected women for prevention of perinatal transmission, it is rarely refused. Additionally, data demonstrate that women with a diagnosis of HIV infection will act to reduce the risk of transmission of HIV to their infants.

Thus, a major hurdle to further reducing the US incidence of perinatal HIV transmission is the number of HIV-infected women who do not have access to adequate prenatal care. Continued decline in perinatal HIV transmission will therefore depend on the success of programs to increase access to and use of prenatal care. Associated with this will be the successful implementation of universal, routine HIV testing, with patient notification of the right of refusal, of pregnant women.

Finally, many HIV-infected women do not receive prenatal care until late in their pregnancy or even during labor and delivery. Thus, success in reducing perinatal transmission of HIV will require the implementation of reliable rapid HIV testing to identify infection in women who present close to or in labor, who have unknown HIV status, and who have not received prenatal care. The implementation of short-course antiretroviral treatments for these women will also be important, as data now indicate that zidovudine and other antiretroviral treatments when administered in partial regimens can reduce perinatal HIV transmission. The need for rapid HIV testing is further supported by evidence that antiretroviral therapy administered to the mother at the onset of labor and to the newborn can also reduce the incidence of perinatal HIV transmission.

THE REPORT OF THE INSTITUTE OF MEDICINE

Introduction

As a result of a commission from Congress (as part of the last Ryan White reauthorization) the IOM in 1999 published a report that extensively examined the issue of perinatal HIV transmission. This report, "Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States," addressed ways to increase prenatal testing, improve therapy for HIV-infected women and children, and generally reduce perinatal HIV infections. The report also considered the ethical and public health issues associated with screening policies as prevention tools, and their implications for the prevention and treatment of HIV in women and infants.

Adoption of a National Policy of Universal HIV Testing

The primary and most important recommendation from the IOM is its endorsement of the adoption of a national policy of universal HIV testing, with patient notification of the right of refusal, as a routine component of prenatal care.

There are two main elements to this recommendation. First, the IOM believes that HIV screening, with patient notification of the right of refusal, should be routine. Thus, the HIV test would be integrated into the battery of tests performed as part of routine prenatal care, and the woman would be informed that the HIV test is being conducted and of her right to refuse it. The IOM believes this approach preserves the doctor-patient relationship and will reduce the barriers to patient acceptance of HIV testing, as the woman would not have to discuss and reveal personal risks that she may perceive as leading to stereotyping. Many physicians use the prenatal visits to provide advice on HIV and sexually transmissible disease prevention, pre-test counseling, and to discuss related personal issues with their patients. The IOM notes that for physicians who may find this embarrassing or difficult, routine testing can remove a potential obstacle to prenatal HIV testing. It would also reduce the physicians' risk of liability when an incorrect guess is made about a woman's risk for HIV infection. The IOM states that, most importantly, this method preserves the woman's right to refuse the test. This right to refuse is also reiterated in the revised recommendations from the USPHS.

The second element of the recommendation is that the screening be universal. If HIV testing applies to all pregnant women regardless of their risk factors and of prevalence rates where they live, the stigma of being a vulnerable person “singled out” for HIV testing would be eliminated. Universal screening also overcomes the problem that many HIV-infected women are missed when a risk- or prevalence-based testing strategy is employed.

Finally, the IOM explains that by incorporating HIV testing into the routine battery of tests performed as part of prenatal care, the costs of the screening would be low and there would be other significant benefits. Universal screening eliminates possible geographic shifts in the epidemiology of perinatal HIV transmission, illustrating that the disease does not have geographic boundaries or genetic predisposition, thereby reducing the stigmatization of specific vulnerable populations. Focusing on the infectious disease aspect of HIV infection allows more open education and communication and prevents a “blame the victim” mentality.

Incorporating This Approach into Prenatal Care

The IOM had several specific recommendations for incorporating universal, routine HIV testing into prenatal care. First, it recommends that health departments, professional organizations, medical specialty boards, regional perinatal HIV centers, and health care plans increase their emphasis on education of prenatal care providers about the value of universal HIV testing and about avenues of referral for patients who test positive.

Second, the IOM acknowledges the impact that specific clinical policies and guidelines from professional organizations have on physicians’ practices, and recommends that professional organizations update their clinical practice guidelines to facilitate universal HIV testing, with patient notification of the right of refusal, as a routine component of prenatal care. Also, it is recommended that all health care plans and providers develop, adopt, and evaluate clinical policies to facilitate universal prenatal HIV testing and that federal funding for state and local efforts to prevent perinatal HIV transmission, including both prenatal testing and care of HIV-infected women, be maintained.

To improve access to prenatal care, the IOM recommends increased efforts to improve coordination of care and access to high-quality HIV interventions and treatment for HIV-positive pregnant women. The IOM notes that without linkage to specialty care, the recommendation for universal HIV testing, with patient notification of the right of refusal, would violate one of the most fundamental criteria for public health screening programs: that there should be adequate facilities for diagnosis and resources for treatment for all who are found to have the condition, as well as agreement as to who will treat them.

The IOM also states that to enhance acceptance of HIV testing, providers need to become aware of the complex myriad of reasons why some pregnant women will refuse testing. Thus, the IOM recommends the development of outreach and education programs to address pregnant women’s concerns about HIV testing and treatment.

The IOM acknowledges that other interventions to prevent perinatal transmission of HIV exist. First, the importance of preventing primary infection of women of childbearing age was emphasized. The IOM recognized that, in particular, programs that target illicit drug users are especially vital for reducing perinatal HIV transmission. Second, averting unintended pregnancy among HIV-infected women is important. The IOM suggests that too many women learn of their HIV status some time in the course of their pregnancy, and thus preconception counseling should provide an opportunity to identify and provide assistance to HIV-infected women who are considering pregnancy. The IOM states clearly that it does not intend to restrict reproductive choice, but notes that interventions for HIV-infected women who choose to terminate their unintended pregnancies can reduce the number of children born with HIV.

Third, the proportion of women, especially drug users, who receive prenatal care must be increased. Thus, the IOM states that efforts to accomplish this should be of high priority. Referring to its report “Prenatal Care: Reaching Mothers, Reaching Infants,” the IOM recommends activities to: (1) remove financial barriers to care; (2) make certain that basic system capacity is adequate for women; (3) improve the policies and practices that shape prenatal services at the delivery site; and (4) increase public information and education about prenatal care.

The IOM also recognizes that labor and delivery represents the last opportunity to interrupt perinatal HIV transmission through administration of antiretroviral therapy and advice to avoid breastfeeding. However, the IOM notes that the time is not ideal for securing consent for HIV testing and for counseling on the implications of a positive result. Thus, the IOM states that any program seeking to implement rapid HIV testing at labor and delivery must consider these issues.

UNIVERSAL, ROUTINE SCREENING WITH PATIENT NOTIFICATION OF THE RIGHT OF REFUSAL VERSUS MANDATORY SCREENING

The controversy over HIV testing of pregnant women has subsided somewhat since the original debate in 1996. There are probably two major reasons: first, the tremendous success that has been demonstrated in reducing perinatal HIV transmission in this country as a result of the implementation of voluntary HIV testing program as originally recommended by the USPHS, and second, the new recommendation from the IOM for universal HIV testing, with patient notification of the right of refusal, as a routine component of prenatal care. In fact, numerous experts in the field of perinatal HIV transmission believe that, with successful implementation of the IOM recommendation, the major hurdle to reducing perinatal transmission of HIV lies in increasing access to adequate prenatal care.

It is obvious that the controversy in the past surrounding HIV screening of pregnant women was related less to the scientific aspects than to the social, ethical, and political implications of testing, particularly mandatory testing. HIV disease and the individuals infected with it have often been subjected to prejudice and discrimination, such that the potential for such effects is enough to separate HIV screening from screening for other maternal infectious diseases. Our AMA's Ethical Opinion on HIV testing states: "Physicians should ensure that HIV testing is conducted in a way that respects patient autonomy and assures patient confidentiality as much as possible... The physician should secure the patient's informed consent specific for HIV testing before testing is performed. Because of the need for pretest counseling and the potential consequences of an HIV test on an individual's job, housing, insurability, and social relationships, the consent should be specific for HIV testing. Consent for HIV testing cannot be inferred from a general consent to treatment..." (E-2.23, AMA Policy Database). It is important to note that a legal requirement for informed consent for prenatal HIV testing, such as those that exist in some states, will actually hinder the implementation of universal HIV testing, with patient notification of the right of refusal, as a routine component of prenatal care.

It has been suggested that mandatory testing for HIV in pregnant women is rational because of the life-and-death issue at stake for the fetus. However, the failure of mandatory premarital HIV testing highlights the important shortcomings of such testing. When mandatory premarital HIV testing was implemented in Illinois, the number of marriage licenses issued greatly declined. Thus, mandatory testing may actually reduce the number of pregnant women seeking prenatal care, especially those in high-risk populations.

Mandatory testing also requires that persons who are identified as HIV-positive be provided medical care and social services follow-up. If pregnant women are required to be tested for HIV, states must be prepared to provide medication and social services when a positive diagnosis occurs. This will further tax already stressed state resources. Along these lines, ethical and legal questions will then arise concerning a state's ability to force a woman to submit to antiretroviral therapy for the benefit of her infant even if she does not want such treatment. Antiretroviral therapy is extremely complex, especially during pregnancy, and requires the active participation of both the patient and her physician. Finally, states would also have to consider the ethical and legal ramifications of whether or not to punish a woman who refuses HIV testing, antiretroviral therapy, or both.

On the other hand, the benefits of universal, routine screening, with patient notification of the right of refusal, are many, as delineated by the IOM and summarized above. Studies indicate that universal screening is cost-effective, acceptable to pregnant women, and can achieve the benefits of prenatal HIV screening without violating women's civil liberties. Additionally, studies have shown that mandatory programs would have the greatest direct costs and place the greatest burden on women's constitutional rights. Finally, studies have also shown that given high levels of acceptance of voluntary HIV testing, now coming to fruition in the United States with the new IOM recommendation, the benefits of mandatory testing are minimal and may lead to avoidance of prenatal care to elude mandatory testing.

POLICIES OF THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, AMERICAN ACADEMY OF PEDIATRICS, AND AMERICAN ACADEMY OF FAMILY PHYSICIANS

In a joint statement released in 1999, ACOG and AAP stated that they:

[S]trongly support efforts to further reduce the rate of perinatal transmission of HIV in the United States. We therefore support the recommendation of the IOM for universal HIV testing with patient notification as a routine component of prenatal care. If a patient declines testing, this should be noted in the medical record. We recognize that current laws in some states may prevent implementation of this recommendation at this time. We encourage our members and Fellows to include counseling as a routine part of care, but not as a prerequisite for and barrier to prenatal HIV testing.

In 2000, ACOG recommended that HIV-positive pregnant women with high viral loads (defined as more than 1,000 copies/mm³) be counseled by physicians about both the benefits and risks of scheduled cesarean delivery to help reduce the rate of perinatal transmission.

In 2001, ACOG released its Committee Opinion 255 "Human Immunodeficiency Virus: Ethical Guidelines for Obstetricians and Gynecologists," which concluded that mandatory prenatal testing is not justifiable ethically.

AAP has the following 1995 policy statement on perinatal HIV Testing:

1. On the basis of recent advances in therapy to reduce the rate of perinatal HIV transmission and the continued occurrence of life-threatening illness in young infants with unrecognized HIV infection, the AAP recommends documented, routine HIV education, and routine testing with consent, for all pregnant women in the United States. Documented consent for maternal and/or newborn HIV testing may be obtained in a variety of ways, including by right of refusal (documented patient education, with testing to take place unless rejected in writing by the patient). The Academy supports utilization of consent procedures that facilitate rapid incorporation of HIV education and testing into the routine medical care setting.
2. Routine education about HIV infection and testing needs to be a part of a comprehensive program of health care for women, particularly for women of child-bearing age.
3. All testing programs for the detection of HIV infection should periodically evaluate the proportion of women who refuse HIV testing following HIV education. Those programs in which a proportionately low number of women receive HIV testing should examine the reasons for poor acceptance, with appropriate program modifications made as needed.
4. For women who are seen by a health care professional for the first time in labor and who have either not received prenatal care or have previously tested negative, but have not been tested for HIV infection during the current pregnancy, education about HIV infection and maternal HIV testing are recommended during the perinatal period.
5. For newborns whose mother's HIV serostatus was not determined during the recent pregnancy or the postpartum period, the infant's health care provider should educate the mother concerning the potential benefits of HIV testing for her infant and the possible risks and benefits to herself of knowing the child's serostatus and recommend HIV testing for the newborn.
6. In the absence of parental availability for consent to test the newborn for HIV antibody, procedures need to be established to facilitate the rapid evaluation and testing of the infant.
7. The health care provider for the infant needs to be informed of maternal HIV serostatus so that appropriate care and testing of the infant can be accomplished. Similarly, if the infant is found to be seropositive when maternal serostatus is unknown, the health care provider for the child should ensure that information about the serostatus and its significance be provided to the mother and, with her consent, to her health care provider. The mother should receive appropriate referral to adult HIV-related services.

8. Comprehensive, HIV-related medical services should be accessible to all infected mothers, their infants, and other family members.
9. The Academy supports legislation and public policy directed toward eliminating any form of discrimination based on HIV serostatus

The American Academy of Family Physicians has the following policy statement on HIV testing of pregnant women:

Pregnant Women: Based upon the recommendations of the CDC and the report of the Institute of Medicine..., the Academy recommends testing for HIV antibody and appropriate counseling for all pregnant women and recognizes the patient's right to refuse testing.

CDC STRATEGIES TO FURTHER REDUCE PERINATAL HIV TRANSMISSION IN THE UNITED STATES

The CDC's current perinatal HIV prevention activities reflect the barriers to reducing perinatal HIV transmission described above. Thus, the CDC is distributing funds to high-prevalence states (over 90% of HIV-infected women live in seven states) to enhance voluntary counseling and testing (VCT) programs. VCT is a cornerstone for early access to prevention as well as to care and support services. The CDC is also actively involved in the USPHS working group that updates the antiretroviral guidelines for pregnant women and has updated CDC guidelines for HIV screening of pregnant women to reflect the IOM's recommendation. The CDC is supporting research into rapid HIV testing and evaluating its possible use during labor and delivery and is also following up on perinatally exposed infants.

As part of the CDC's plan to further reduce perinatal transmission, it will be improving its surveillance activities and expanding HIV reporting to all states. The CDC will support additional operational research to improve implementation of interventions during the intrapartum period and will continue to educate health care providers regarding universal, routine HIV testing of pregnant women. The CDC will also advocate for and support HIV testing of pregnant women as a Health Employer Data and Information Set (HEDIS) measure and will promote model Medicaid-managed care contract language.

The CDC states that it will direct primary prevention programs at youth and women of childbearing age and will continue to seek congressional funding to enhance VCT programs and services to pregnant women. Studies are being planned to evaluate where opportunities to reduce perinatal HIV transmission are being missed and also to examine possible interventions when cases of perinatal AIDS do occur. As research demonstrates the value of rapid testing, the CDC will work to expand availability of such testing for women with unknown HIV status presenting in labor. Significantly, the use of rapid HIV testing will also be useful in the prenatal setting, especially for testing women who might be unlikely to return for test results. Finally, the CDC will develop approaches for long-term monitoring of infants who were exposed to antiretroviral therapy perinatally. Significantly, lessons learned in the United States will be important for global efforts to reduce perinatal HIV transmission.

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following statements be adopted and that the remainder of this report be filed.

1. That American Medical Association Policy H-20.930, "Counseling and Testing of Pregnant Women for HIV," be amended by insertion and deletion to read as follows:

~~The Our~~ AMA supports the position that there should be ~~mandatory universal~~ HIV testing of all pregnant women ~~and newborns, with patient notification of the right of refusal, as a routine component of prenatal care, and that such testing should be accompanied by basic counseling and recommendations for awareness of appropriate treatment, if necessary. Patient notification should be consistent with the principles of informed consent.~~

2. That AMA Policy H-20.931, "Maternal HIV Screening and Treatment to Reduce the Risk of Perinatal HIV Transmission," be amended by insertion and deletion to read as follows:

~~An Update Report:~~—In view of the significance of the finding that ~~zidovudine~~ treatment of HIV-infected pregnant women with appropriate antiretroviral therapy can reduce the risk of transmission of HIV to their infants, ~~the~~ our AMA recommends the following statements:

- (1) Given the prevalence and distribution of HIV infection among women in the United States, the potential for effective early treatment of HIV infection in both women and their ~~children~~ infants, and the significant reduction in perinatal HIV transmission with treatment of pregnant women with ~~zidovudine~~ appropriate antiretroviral therapy, routine education about HIV infection and testing should be part of a comprehensive health care program for it is important for physicians to give a high priority to educating all women about HIV infection and, particularly for those who are pregnant or who may become pregnant, to strongly encourage them to have HIV antibody testing. The ideal would be for all women to know their HIV status before ~~becoming pregnant~~ considering pregnancy.
- (2) Universal HIV testing of all pregnant women, with patient notification of the right of refusal, should be a routine component of prenatal care. Basic counseling on HIV prevention and treatment should also be provided to the patient, consistent with the principles of informed consent.
- (2) (3) The final decision about accepting HIV testing is the responsibility of the woman. ~~The d~~Decision to consent to or refuse an HIV test should be voluntary ~~and should follow appropriate education.~~ When the choice is to reject testing, the patient's refusal may should be asked to record her refusal on the patient's recorded. Test results should be confidential within the limits of existing law and the need to provide appropriate medical care for the woman and her ~~baby~~ infant.
- (3) (4) To assure that the intended results are being achieved, the proportion of pregnant women ~~who have received education about HIV infection and~~ who have accepted or rejected HIV antibody testing and follow-up care should be monitored and reviewed periodically at the appropriate practice, program or institutional level. Programs in which the proportion of women accepting HIV testing is low should evaluate their ~~education efforts and~~ methods to determine how they can achieve ~~higher~~ greater success.
- (4) (5) Women who are not seen by a health care professional for prenatal care until late in pregnancy or after the onset of labor should receive education about HIV infection and be encouraged to have be offered HIV testing at the earliest practical time, but not later than during the immediate postpartum period.
- (5) (6) When HIV infection is documented in a pregnant woman, ~~she should be provided with proper post-test counseling should be provided.~~ The patient should be given an appropriate medical evaluation of the stage of infection and ~~be given~~ full information about the recommended management plan for her; own health. Information should be provided about the potential for reducing the risk of perinatal transmission of HIV infection to her baby infant through the use of antiretroviral therapy, and about the potential but unknown long-term risks to herself and her baby infant from the treatment course. The final decision to accept or reject zidovudine antiretroviral treatment recommended for herself and her child infant is the right and responsibility of the woman. When the woman's serostatus is either unknown or known to be positive, appropriate counseling should also be given regarding the risks associated with breastfeeding for both her own disease progression and disease transmission to the infant.
- (6) (7) Appropriate medical treatment for HIV-infected pregnant women should be determined on an individual basis using the latest published Public Health Service (PHS) recommendations. The most appropriate care should be available regardless of the stage of HIV infection or the time during gestation at which the woman presents for prenatal or intrapartum care.
- (7) (8) To facilitate optimal medical care for ~~both~~ women and their infants, HIV ~~antibody~~ test results (both positive and negative) and associated management information should be available to the physicians taking care of both mother and infant. Ideally this information will be included in the confidential medical records. Physicians providing care for a woman or her infant should obtain the appropriate consent and should notify the other involved physicians of the HIV status of and management information about the mother and infant, consistent with applicable state law.

- (8) (9) ~~To provide a better knowledge base to improve medical care in the future, it is essential that Continued research into new interventions is essential to further reduce the perinatal transmission of HIV, particularly the use of rapid HIV testing for women presenting in labor and for women presenting in the prenatal setting who may not return for test results. The studies be developed and implemented to document quantitatively and qualitatively any long-term effects of zidovudine antiretroviral therapy during pregnancy and the peripartum intrapartum period for both women and their infants also must be evaluated.~~ For both infected and uninfected infants exposed to perinatal antiretroviral treatment, long-term follow-up studies are urgently needed to assess potential complications such as organ system toxicity, neurodevelopmental problems, pubertal development problems, reproductive capacity, and development of neoplasms.
- (10) Health care professionals should be educated about the benefits of universal HIV testing, with patient notification of the right of refusal, as a routine component of prenatal care, and barriers that may prevent implementation of universal HIV testing as a routine component of prenatal care should be addressed and removed. Federal funding for efforts to prevent perinatal HIV transmission, including both prenatal testing and appropriate care of HIV-infected women, should be maintained.
3. That our AMA support the recommendations of the Institute of Medicine's report on perinatal HIV transmission, "Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States."
4. That AMA Policy H-20.973, "Neonatal HIV Antibody Screening," be amended by insertion and deletion to read as follows:
- Our AMA:
- (1) urges the US Public Health Service to rapidly pursue the ~~development~~ implementation of confirmatory tests and procedures for more accurate demonstration of HIV infection in the newborn;
- (2) supports HIV antibody testing of the newborn in states with a high prevalence of HIV infection on a voluntary basis with maintenance of strict confidentiality. ~~Such testing should be routinely offered (i.e., provider initiated) to all pregnant women living in these areas and appropriate pre- and post-test counseling must be provided;~~
- (3) ~~believes such voluntary testing for HIV infection should be routinely available upon patient request to all other pregnant women;~~
- (4) (3) favors giving consideration to supporting mandatory rapid HIV testing of all newborns for HIV infection, with maternal consent, when the maternal HIV status has not been determined during pregnancy or labor when treatment modalities with potential benefit for infected neonates become available.
5. That AMA Policy H-20.988, "Prevention and Control of AIDS," paragraph [2], be amended by insertion and deletion to read as follows:
- (2) Voluntary testing should be regularly provided for the following types of individuals who give an informed consent: (a) Patients at sexually transmissible disease clinics. (b) Patients at drug abuse clinics. (c) ~~Pregnant women in high risk areas in the first trimester of pregnancy.~~ (d) Individuals who are from areas with a high incidence of AIDS or who engage in high risk behavior seeking family planning services. ~~(e) (d) Patients who are from areas with a high incidence of AIDS or who engage in high risk behavior requiring surgical or other invasive procedures. If the voluntary policy is not sufficiently accepted, the hospital and medical staff should consider a mandatory program for the institution. In addition, universal HIV testing of all pregnant women, with patient notification of the right of refusal, should be a routine component of prenatal care.~~
6. That AMA Policies H-20.927, "Counseling and Testing of Pregnant Women for HIV," H-20.932, "HIV Counseling and Testing of Pregnant Women," and H-20.933, "Maternal HIV Screening and Treatment to Reduce Risk of Personal HUV Transmission," be rescinded, and that Policy H-20.964, "Options for Pregnant HIV-Seropositive Women," paragraphs [1] and [2] also be rescinded, with paragraph [3] retained.
7. That our AMA's Council on Scientific Affairs prepare a policy consolidation report that will consolidate current AMA policy on HIV.

APPENDIX A - EXISTING AMA POLICY ON PERINATAL HIV TRANSMISSION

H-20.927 Counseling and Testing of Pregnant Women for HIV

Policy of the AMA states that physicians and other health care providers who are principally responsible for the prenatal care and delivery have a mandatory responsibility to provide information and counseling to pregnant women about the risk of vertical transmission of human immunodeficiency virus (HIV) and the benefits of treatment and a responsibility to document such counseling, testing and treatment results. (Sub. Res. 421, I-96)

H-20.930 Counseling and Testing of Pregnant Women for HIV

The AMA supports the position that there should be mandatory HIV testing of all pregnant women and newborns with counseling and recommendations for appropriate treatment. (Res. 425, A-96)

H-20.931 Maternal HIV Screening and Treatment to Reduce the Risk of Perinatal HIV Transmission

An Update Report: In view of the significance of the finding that zidovudine treatment of HIV-infected pregnant women can reduce the risk of transmission of HIV to their infants, the AMA recommends the following statements:

- (1) Given the prevalence and distribution of HIV infection among women in the United States, the potential for effective early treatment of HIV infection in both women and their children, and the significant reduction in perinatal HIV transmission with treatment of pregnant women with zidovudine, it is important for physicians to give a high priority to educating all women about HIV infection and, particularly for those who are pregnant or who may become pregnant, to strongly encourage them to have HIV antibody testing. The ideal would be for all women to know their HIV status before becoming pregnant.
- (2) The final decision about accepting HIV testing is the responsibility of the woman. Decision to consent to or refuse an HIV test should be voluntary and should follow appropriate education. When the choice is to reject testing, the patient may be asked to record her refusal on the patient's record. Test results should be confidential within the limits of existing law and the need to provide appropriate medical care for the woman and her baby.
- (3) To assure that the intended results are being achieved, the proportion of pregnant women who have received education about HIV infection and who have accepted or rejected antibody testing and follow-up care should be monitored and reviewed periodically at the appropriate practice, program or institutional level. Programs in which the proportion of women accepting HIV testing is low should evaluate their education efforts and methods to determine how they can achieve higher success.
- (4) Women who are not seen by a health care professional for prenatal care until after the onset of labor should receive education about HIV infection and be encouraged to have HIV testing at the earliest practical time, but not later than during the immediate postpartum period.
- (5) When HIV infection is documented in a pregnant woman, she should be provided with an appropriate medical evaluation of the stage of infection and be given full information about the recommended management plan for her, the potential for reducing the risk of perinatal transmission of HIV infection to her baby, and the potential but unknown long-term risks to herself and her baby from the treatment course. The final decision to accept or reject zidovudine treatment recommended for herself and her child is the right and responsibility of the woman.
- (6) Appropriate medical treatment for HIV-infected pregnant women should be determined on an individual basis using the published PHS recommendations. The most appropriate care should be available regardless of the stage of HIV infection or the time during gestation at which the woman presents for prenatal or intrapartum care.
- (7) To facilitate optimal medical care for both women and their infants, HIV antibody test results (both positive and negative) and associated management information should be available to the physicians taking care of both mother and infant. Ideally this information will be included in the confidential medical records. Physicians providing care for a woman or her infant should obtain the appropriate consent and should notify the other involved physicians of the HIV status of and management information about the mother and infant.
- (8) To provide a better knowledge base to improve medical care in the future, it is essential that studies be developed and implemented to document quantitatively and qualitatively any long-term effects of zidovudine therapy during pregnancy and the peripartum period for both women and their infants. For both infected and uninfected infants, long-term follow-up studies are urgently needed to assess potential complications such as organ system toxicity, neurodevelopmental problems, pubertal development problems, reproductive capacity, and development of neoplasms. (CSA Rep. 6-A-95)

H-20.932 HIV Counseling and Testing of Pregnant Women

Policy of the AMA states that HIV counseling and testing shall be offered to all pregnant women as a standard practice. (Res. 415, I-94; Reaffirmed by Rules & Credentials Cmt., A-96)

H-20.933 Maternal HIV Screening and Treatment to Reduce Risk of Personal HIV Transmission

The AMA recommends:

- (1) Since preliminary results of a study of antiretroviral therapy in HIV-infected pregnant women have shown that treatment can reduce the risk of transmission of HIV from infected mothers to their neonates, physicians providing care for women who are pregnant or who may become pregnant should discuss HIV infection with these women and encourage them to have HIV antibody testing.
- (2) Physicians should assess each pregnant woman for risk of HIV infection as part of routine prenatal care, recognizing that heterosexual sexual contact can be a significant risk for HIV infection.
- (3) While all pregnant women should be provided information about HIV infection by their physicians and encouraged to have HIV antibody testing, pregnant women who are identified as having a specific risk for HIV infection should be more intensively educated and strongly encouraged to have HIV antibody testing. In particular, pregnant women who live in a community in which the prevalence of HIV infection is high (eg, a prevalence of HIV infection of 1.0% or more in the total population or a prevalence of HIV infection of 0.05% or more of women of childbearing age) should be encouraged to have antibody counseling and testing. Risk factors for HIV infection include, but are not limited to, the following: (a) A history of illicit injection drug use, particularly if needles or other infection equipment have been shared, or if used or unsterile equipment has been used; (b) Past or present sex partners who are known or suspected to be HIV infected; (c) Sexual contact without protection (such as a condom), particularly with multiple partners or with a person who is at risk of HIV infection; (d) A history of or current infection with a sexually transmitted disease; (e) A history of receiving blood transfusions between 1978 and 1985, or a history of a clotting factor disorder, such as hemophilia, requiring treatment with blood products between 1978 and 1985; (f) Origin in another country in which the prevalence of HIV infection is high; and (g) Medical symptoms consistent with HIV-related illness.
- (4) Post-test counseling for a pregnant woman with HIV infection should include current information about the potential for zidovudine treatment during pregnancy to reduce the risk of perinatal HIV transmission to her infant. Information about the potential for risks of adverse events secondary to treatment also should be discussed.
- (5) Medical evaluation should be arranged for all HIV-infected women to help determine what type of medical care is appropriate. If a woman's stage of HIV infection does not require zidovudine therapy, the use of zidovudine treatment during pregnancy to reduce risk of perinatal HIV transmission should be discussed and a decision about treatment reached jointly with the woman. In the case of a woman who has not had prenatal care, and who may even be in labor, the use of zidovudine to reduce the risk of intra-partum or post-partum transmission is, again, a matter of discussion and decision with the woman. (CSA Rep. 7-A-94; Reaffirmed by Rules & Credentials Cmt., A-96)

H-20.964 Options for Pregnant HIV-Seropositive Women

Our AMA:

- (1) continues to support the education, screening, and counseling of women at high risk for HIV infection;
- (2) continues to support the counseling of HIV seropositive pregnant women on all medically appropriate alternatives; and
- (3) supports government funding of all medical services that are deemed appropriate by both the patient and physician for pregnant seropositive women lacking other sources of funding. (Res. 12, I-89; Reaffirmed: Sunset Report, A-00)

H-20.973 Neonatal HIV Antibody Screening

Our AMA:

- (1) urges the US Public Health Service to rapidly pursue the development of confirmatory tests and procedures for more accurate demonstration of HIV infection in the newborn;
- (2) supports HIV antibody testing of the newborn in states with a high prevalence of HIV infection on a voluntary basis with maintenance of strict confidentiality. Such testing should be routinely offered (i.e., provider initiated) to all pregnant women living in these areas and appropriate pre- and post-test counseling must be provided;

- (3) believes such voluntary testing for HIV infection should be routinely available upon patient request to all other pregnant women;
- (4) favors giving consideration to supporting mandatory testing of all newborns for HIV infection, when treatment modalities with potential benefit for infected neonates become available. (BOT Rep. Q, A-89; Reaffirmed: Sunset Report, A-00)

H-20.977 Reducing Transmission of Human Immunodeficiency Virus (HIV)

....(7) Urges development of educational, medical, and social support programs for pregnant IVDA's and those who may become pregnant to address the current and future health care needs of both mothers and newborns. Further, the AMA advocates development of optimal care programs for HIV-positive and AIDS-symptomatic infants and their families. Such programs should include support systems to help parents care for these infants and simplified foster care arrangements for children whose parents are unable to provide such care.... (CSA Rep. C, A-88; Amended: BOT Rep. 34-I-93; Reaffirmation I-96; Reaffirmed: CSA Rep. 12-A-99)

H-20.988 Prevention and Control of AIDS

....(2) Voluntary testing should be regularly provided for the following types of individuals who give an informed consent: (a) Patients at sexually transmitted disease clinics. (b) Patients at drug abuse clinics. (c) Pregnant women in high risk areas in the first trimester of pregnancy. (d) Individuals who are from areas with a high incidence of AIDS or who engage in high risk behavior seeking family planning services. (e) Patients who are from areas with a high incidence of AIDS or who engage in high risk behavior requiring surgical or other invasive procedures. If the voluntary policy is not sufficiently accepted, the hospital and medical staff should consider a mandatory program for the institution.... (BOT Rep. YY, A-87; Modified: Sunset Report, I-97)

APPENDIX B - PUBLIC HEALTH SERVICE TASK FORCE RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL DRUGS IN PREGNANT HIV-1-INFECTED WOMEN FOR MATERNAL HEALTH AND INTERVENTIONS TO REDUCE PERINATAL HIV-1 TRANSMISSION IN THE UNITED STATES

May 4, 2001

Summary

These recommendations update the January 24, 2001 guidelines developed by the Public Health Service for the use of zidovudine (ZDV) to reduce the risk for perinatal human immunodeficiency virus type 1 (HIV-1) transmission*. This report provides health care providers with information for discussion with HIV-1 infected pregnant women to enable such women to make an informed decision regarding the use of antiretroviral drugs during pregnancy and use of elective cesarean delivery to reduce perinatal HIV-1 transmission. Various circumstances that commonly occur in clinical practice are presented as scenarios and the factors influencing treatment considerations are highlighted in this report. It is recognized that strategies to prevent perinatal transmission and concepts related to management of HIV disease in pregnant women are rapidly evolving. The Perinatal HIV Guidelines Working Group will review new data on an ongoing basis and provide regular updates to the guidelines; the most recent information is available on the HIV/AIDS Treatment Information Service (ATIS) website (www.hivatis.org).

In February 1994, the results of Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 documented that ZDV chemoprophylaxis could reduce perinatal HIV-1 transmission by nearly 70%. Epidemiologic data have since confirmed the efficacy of ZDV for reduction of perinatal transmission and have extended this efficacy to children of women with advanced disease, low CD4+ T-lymphocyte counts, and prior ZDV therapy. Additionally, substantial advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. These advances have resulted in changes in standard antiretroviral therapy for HIV-1 infected adults. More aggressive combination drug regimens that maximally suppress viral replication are now recommended. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy. The use of antiretroviral drugs in pregnancy requires unique considerations, including the potential need to alter dosing as a result of physiologic changes associated with pregnancy, the potential for adverse short- or long-term effects on the fetus and newborn, and the effectiveness for reducing the risk for perinatal transmission. Data to address many of these considerations are not yet available. Therefore, offering antiretroviral therapy to HIV-1-infected women during pregnancy, whether primarily to treat HIV-1 infection, to reduce perinatal transmission, or for both purposes, should be accompanied by

a discussion of the known and unknown short- and long-term benefits and risks of such therapy for infected women and their infants. Standard antiretroviral therapy should be discussed with and offered to HIV-1 infected pregnant women. Additionally, to prevent perinatal transmission, ZDV chemoprophylaxis should be incorporated into the antiretroviral regimen.

* - Information included in these guidelines may not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

(References pertaining to Report 1 of the Council on Scientific Affairs are available from the Group Office on Science, Quality and Public Health.)

2. MARKETING AND CLINICAL USE OF INHALED NITRIC OXIDE (RESOLUTION 417, I-00)

HOUSE ACTION: RECOMMENDATION ADOPTED AND REMAINDER OF REPORT FILED

INTRODUCTION

Resolution 417, introduced by the Oregon Delegation and referred to the Board of Trustees at the 2000 Interim Meeting, asks:

That our American Medical Association express its concern to government authorities over the pricing of inhaled nitric oxide (iNO) and the method of marketing of the device for its administration; and

That our AMA ask the Food and Drug Administration and the Federal Trade Commission to review the marketing practices used to make this drug available for critically ill patients.

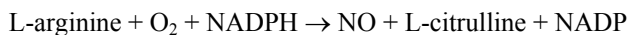
Testimony provided at the Reference Committee also noted that the efficacy of nitric oxide therapy, including potential off-label uses, should be evaluated in this report.

METHODS

Literature searches were conducted in the MEDLINE database for English-language articles published between 1990 and September 2001 using the search term "nitric oxide" in combination with "administration and dosage," "adverse effects," "diagnostic use," "therapeutic use," and "human," but not "air pollution" or "animal." The Cochrane Library of Systematic reviews and randomized controlled trials was searched using the term "nitric oxide," which identified 3 existing systematic reviews on the use of nitric oxide for respiratory failure in preterm infants, infants born at or near term, and in children and adults suffering from acute hypoxemic respiratory failure. Additional references were culled from the bibliographies of these references. In addition, the manufacturer (INO Therapeutics) of inhaled nitric oxide (INOMax[®]) was contacted for relevant information on the marketing of this substance.

BACKGROUND

Previously seen as a noxious pollutant and poison, nitric oxide (NO) plays a vital role in many physiologic processes, including vasodilation, neurotransmission, and inflammation. In vivo, NO accounts for the activity of endothelium-derived releasing factor. It is derived from L-arginine in a one-step process synthesized by NO synthase in endothelium, neurons, and leukocytes. Leukocyte-derived NO synthase is inducible during infection and inflammation.



Nitric oxide dilates vascular smooth muscle, suppresses platelet adhesion/aggregation and leukocyte migration/adhesion, attenuates vascular smooth muscle proliferation, and under certain conditions exhibits anti-inflammatory and anti-oxidant properties. Nitric oxide inhaled in high concentrations causes methemoglobinemia and is converted to NO₂, which exerts oxidant and cytotoxic effects.

Physiologically, NO binds to the heme moiety of soluble guanyl cyclase, increasing the concentration of cyclic GMP, which relaxes vascular smooth muscle. Diminished NO synthesis, increased destruction, or reduced cellular sensitivity to its effects are associated with advanced age and have been noted in patients with hyperlipidemia, atherosclerosis, hypertension, chronic renal failure, and diabetes mellitus. Endogenous NO appears to play an important role in the transition to pulmonary circulation at birth and in the regulation of pulmonary vascular resistance.

Disposition and Toxicity of Inhaled Nitric Oxide. Between 75% to 90% of inhaled nitric oxide (iNO) is taken up by pulmonary capillary beds where it combines (predominately) with oxyhemoglobin to produce methemoglobin (MetHb). The latter is metabolized by methemoglobin reductase to hemoglobin and nitrate. Most of the absorbed NO is eventually eliminated as nitrate via glomerular filtration.

Nitric oxide is an evanescent compound with a half-life of ≤40 seconds. The reaction of NO with oxyhemoglobin limits the systemic effects of iNO, which tends to dilate only those vessels directly adjacent to alveoli that are being ventilated. At low oxygen saturation, NO can combine with deoxyhemoglobin, forming a nitrosylhemoglobin intermediate that, in the presence of O₂ converts to MetHb and nitrogen oxide. Nitric oxide also can combine with oxygen and water to form nitrogen dioxide and nitrite, respectively, which also can interact with oxyhemoglobin to produce MetHb and nitrate. Methemoglobin levels remain below 1% and NO₂ concentrations are generally <0.5 ppm when NO is administered at concentrations of 5 to 20 ppm. In patients receiving larger doses of iNO (80 ppm), MetHb levels may exceed 7%, and mean NO₂ values may exceed 2.5 ppm. Monitoring for PaO₂, methemoglobin, and NO₂ should accompany NO administration.

Nitric oxide can also form other cytotoxic intermediates such as peroxynitrite and nitrotyrosine in the presence of superoxide anion. Both NO and NO₂ are potentially directly toxic, capable of causing pulmonary edema and hypoxemia. Because NO inhibits platelet aggregation, it also increases bleeding time in neonates and adults.

FDA APPROVAL OF INHALED NITRIC OXIDE

The Drug. Inhaled nitric oxide (INOmax[®]) was approved as an orphan drug in December 1999 for use in near-term and term infants (>34 weeks) with hypoxemic respiratory failure associated with clinical or electrocardiographic evidence of pulmonary hypertension. The orphan product designation carries with it a 7-year patent exclusivity for the use of iNO. Inhaled nitric oxide improves oxygenation in these infants and reduces the need for extracorporeal membrane oxygenation (ECMO), an effective but invasive procedure with significant potential morbidity and mortality. INOmax[®] is a gaseous blend of NO (0.1% or 0.8%) and nitrogen (99.9% or 99.2%) that is supplied in aluminum cylinders as a compressed gas.

FDA approval was based on studies in neonates up to 14 days of age. The recommended dose is 20 ppm. Treatment should be maintained for up to 14 days or until the underlying oxygen desaturation has resolved and the neonate can be weaned from iNO therapy. In clinical trials, the NO delivery systems provided operator-determined concentrations of NO in the breathing gas, and the concentration was constant throughout the respiratory cycle. The FDA specified that INOmax[®] must be delivered through a system with these characteristics and which does not cause generation of excessive inhaled nitrogen dioxide. Inspired NO and NO₂ must be monitored using a properly calibrated analysis device with alarms. The concentration of NO₂ is dependent on the concentration of NO delivered, the concentration of oxygen with which it mixes, and the residence time in the delivery circuit. This system should be calibrated using a precisely defined calibration mixture of NO and NO₂.

The Device. At the time the FDA approved INOmax[®], no devices were approved for the delivery and monitoring of this potentially noxious substance. On January 6, 2000, the FDA issued an order classifying the Datex-Ohmeda's device (INOvent[®] Delivery System) as a Class III device. Such devices are not substantially equivalent to devices that were introduced or delivered for introduction into interstate commerce for commercial distribution before 1976, or to a device that was subsequently reclassified into Class I or Class II. On January 7, 2000, Datex-Ohmeda submitted a petition requesting classification of the components of the INOvent[®] delivery system.

On January 11, 2000, the FDA issued an order to Datex-Ohmeda classifying the INOvent[®] Delivery System as a Class II device with special controls. The delivery system consists of 3 devices, to which the FDA assigned the generic names “nitric oxide administration apparatus,” “nitric oxide analyzer,” and “nitrogen dioxide analyzer.” The special control developed by the agency is a guidance document, the purpose of which is to facilitate the preparation and the review of premarket notifications for the NO delivery apparatus, NO analyzers, and NO₂ analyzers, 3 devices that may be separately manufactured.

MARKETING OF INOMAX[®]

The marketing of INOmax[®] is based on method-of-use patents licensed by INO Therapeutics from Massachusetts General Hospital (personal communication, Ashleigh Palmer, INO Therapeutics, August 2001). The patents cover both use of the gas and the device for delivering and monitoring NO for immediate inhalation into the ventilatory circuit. In North America, the INOvent[®] delivery system is currently available under exclusive license through INO Therapeutics. To ensure safe and effective delivery of the therapy, INO Therapeutics offers INOmax[®] as part of a commercial package, called INOtherapy[™], which includes the following components: INOmax[®] (nitric oxide) for inhalation, INOvent[®] delivery system, INOcal[®] calibration mixtures, and the INO Therapeutics service. The INOvent[®] system was selected for ease and simplicity of use, its safety record, and its compatibility with various ventilators in common use (personal communication, Ashleigh Palmer, INO Therapeutics, August, 2001).

During the 1990s and prior to approval of INOmax[®], INO Therapeutics provided the iNO free of charge to sites and investigators operating under an Investigational New Drug Application. After FDA approval, the gas and delivery device and services were made available to “inhaled nitric oxide ready” facilities. During the initial marketing phase of this product, services included stocking of NO cylinders, and at least 2 devices. When therapy needed to be initiated, the company was notified, and supplied at least one additional device for back-up and additional cylinders at a cost of \$3,000/day/patient regardless of the duration of use. One hundred eight delivery centers are maintained nationwide, capable of reaching any center within 2 hours. This practice and price created a backlash among practitioners and hospitals who had been getting the drug free and fostered the impression that the company was taking advantage of a monopoly situation by bundling the product, device, and maintenance agreements. The cost has been justified on economic grounds, given the high costs of ECMO, which iNO reduces the need for, in properly selected patients. In one limited, short-term cost-effectiveness analysis of the use of iNO versus oxygen administered to near-term infants with severe respiratory illness who were referred for consideration of ECMO, the cost-effectiveness ratio for iNO was approximately \$23,000 per life saved. Additional pharmacoeconomic studies are needed within the framework of clinical practice to place the current cost of NO therapy in proper perspective. Subsequently, INO Therapeutics has modified the unitary charge approach. Administration devices are now equipped with a timing device that records the actual duration of administration. Instead of a flat \$3,000/day fee per patient, hospitals are charged a usage fee at a rate of \$125/hour, regardless of the number of patients who might receive therapy in a given day from a given cylinder.

CLINICAL USES OF INHALED NITRIC OXIDE

Nitric Oxide for Respiratory Failure in Infants Born at or Near Term

Persistent pulmonary hypertension of the newborn (PPHN) is an important cause of cardiorespiratory failure, either as a primary condition or secondary to hyaline membrane disease, meconium aspiration, infection, congenital diaphragmatic hernia, and other diverse cardiac and pulmonary disorders. The syndrome is characterized by high pulmonary vascular resistance that causes extrapulmonary right-to-left shunting of blood across the ductus arteriosus, the foramen ovale, or both. It is the most common factor in infants who require treatment with ECMO. Recent evidence indicates that infants with persistent pulmonary hypertension have low plasma concentrations of arginine (the precursor for NO) and NO metabolites, a pattern that is based on the genetically determined capacity of the urea cycle, which normally supplies arginine as an intermediate.

Prior to the use of iNO, conventional therapies included high concentrations of inspired oxygen, hyperventilation, high-frequency ventilation, induction of alkalosis, use of positive inotropic agents, systemic vasodilators, paralysis and sedation. Results have been mixed at best. None of the above therapies has been proven by prospective randomized trials to reduce mortality or the need for ECMO. Much of the morbidity and mortality in neonatal lung diseases results from therapies targeted at enhancing gas exchange (e.g., bronchopulmonary dysplasia as a result of mechanical ventilation, oxygen toxicity, and the risks inherent in ECMO).

The physiologic effects of iNO were first reported in infants with PPHN in 1992. The early indication was that some neonates could avoid ECMO as a result of iNO. Subsequently, 11 randomized trials have been conducted that analyzed outcomes in term or near-term infants (>34 weeks gestation) with hypoxemia due to either lung disease or pulmonary hypertension with right-to-left shunting who were treated with iNO.

In the seven trials that reported on subsequent requirements for ECMO, meta-analysis showed a significant effect of iNO in reducing this intervention and a reduction in the combined outcome of death or requirement for ECMO. When analyzed separately, none of the eight trials that reported mortality data found a significant effect, nor did the meta-analysis. Most studies found large increases in PaO₂ within 30 to 60 minutes after treatment and significant improvements in the oxygenation index. The use of high frequency oscillatory ventilation plus iNO may be more successful than either treatment alone.

Large increases in oxygenation in response to iNO probably represent reversal of extrapulmonary right-to-left shunting of blood secondary to pulmonary vasodilation; lesser improvements in oxygenation represent improvement in ventilation-perfusion matching secondary to redistribution of pulmonary blood flow to well-ventilated lung regions. Infants with diaphragmatic hernia do not appear to share these benefits of iNO. Limited controlled data indicate that survivors treated with iNO have comparable neurodevelopmental outcomes, consistent with previous uncontrolled reports. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary diseases, or neurological sequelae.

Information available at this time suggests that iNO therapy in hypoxemic term or near-term neonates decreases their need for ECMO. Inhaled nitric oxide also can improve oxygenation in some newborns with hypoxemia who have V/Q disturbances or intrapulmonary right-to-left shunting, although effects may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease. It is not known whether earlier intervention may improve mortality.

Unlabeled Uses

The American Academy of Pediatrics recommends that administration of iNO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remain experimental. As such, iNO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed consent. Generally, use should be offered only at centers that are qualified to provide multisystem support, including on-site ECMO capability. If ECMO is not available on site, mechanisms for timely transfer of infants to a collaborating ECMO center should be established; transfer must be accomplished without interruption of iNO therapy, given the potential for progressive worsening of oxygenation upon abrupt withdrawal of iNO.

Inhaled Nitric Oxide for Respiratory Failure in Preterm Infants

Since the introduction of surfactant, mortality from respiratory failure in preterm infants has fallen significantly. However, some infants do not have adequate improvement in oxygenation following surfactant treatment. Three randomized trials have examined the use of inhaled nitric oxide in preterm infants who had either a high risk of developing bronchopulmonary dysplasia, a 50% predicted mortality, or oxygenation indices between 12.5 and 30. Although short-term improvement in oxygenation may occur (and one study showed a reduction in days receiving assisted ventilation), iNO had no significant effect on mortality, the incidence of intraventricular hemorrhage, or the occurrence of bronchopulmonary dysplasia. Current evidence does not support the use of iNO in preterm infants with hypoxemic respiratory failure. However, three multicenter trials are currently investigating the potential use of iNO in preterm infants.

Inhaled Nitric Oxide for Acute Hypoxemic Respiratory Failure in Children and Adults

Acute hypoxemic respiratory failure (AHRF) occurs in patients with acute respiratory distress syndrome (ARDS), acute lung injury, or other causes of hypoxemic respiratory failure. Hypoxemia is a consequence of ventilation/perfusion mismatch. Because mortality in AHRF is often due to the primary disease process rather than hypoxemia per se, treatments aimed at improving lung oxygenation may not affect ultimate outcome. ARDS is defined as acute onset of non-cardiac pulmonary disease in patients >1 month of age, associated with diffuse, bilateral pulmonary infiltrates on chest radiograph, a pulmonary wedge pressure of 18 mm Hg or absent left atrial enlargement, and hypoxemia defined by a hypoxia score (PaO₂/FiO₂) less than 200 mg Hg, irrespective of positive

end-expiratory pressure. Acute lung injury incorporates a hypoxia score between 200 and 300 mg Hg in addition to the other ARDS criteria. When the ARDS criteria are not fulfilled, patients experiencing respiratory failure have “hypoxemic respiratory failure.”

Five peer-reviewed, published randomized trials have been conducted in children or adults with AHRF that: (1) compared iNO with “inhaled placebo” or no treatment and maximal conventional ventilator therapy; (2) obtained data during and after therapy; and (3) did not employ multiple cross-over arms. Outcome measures included improvement in oxygenation as measured by the oxygenation index and hypoxia scores (PaO₂/FiO₂), ventilator-free days over a 30-day period, duration of stay in the hospital or intensive care unit, and mortality. Temporary improvements in arterial oxygenation in the first 24 hours of treatment were reported, but no significant differences in mortality or other clinical indicators of effectiveness have been realized.

Other Unlabeled Uses

Case reports and case series have noted potential utility of iNO in a number of other conditions including the treatment of pulmonary hypertension following cardiopulmonary bypass or the use of a ventricular assist device, for mitral valve replacement, coronary bypass graft, heart or lung transplantation, and for pulmonary embolism. Also, iNO has been used for the treatment of respiratory failure in children with serious burns, and in patients undergoing lung transplantation, or suffering from progressive congestive heart failure, status asthmaticus, sickle cell acute chest syndrome, or high-altitude pulmonary edema.

Use in infants with congenital heart disease is controversial. In one small randomized trial, iNO did not substantially improve pulmonary hemodynamics and gas exchange immediately after operation for congenital heart disease and did not significantly decrease the incidence of pulmonary hypertensive crises. Another small randomized controlled trial found that low doses of iNO decreased the incidence of pulmonary hypertensive crises in infants treated after congenital heart surgery.

Although product labeling warns against use of iNO in pregnancy, case reports have noted beneficial effects for the treatment of pregnancy-associated pulmonary hypertension or Eisenmenger syndrome. Inhaled nitric oxide does not improve function in patients with exacerbation of chronic obstructive pulmonary disease.

SUMMARY AND CONCLUSION

Inhaled nitric oxide is effective in decreasing the requirement for ECMO in term and near-term neonates with persistent pulmonary hypertension. Beneficial effects on mortality have not been shown, but studies are underway to evaluate the earlier use of iNO in these infants. Inhaled nitric oxide has been used in the treatment of acute hypoxemic respiratory failure in preterm infants, as well as older children and adults. Use in these patients and for several other conditions remains promising but experimental.

The marketing of INOmax[®] is based on method-of-use patents. Preliminary pharmacoeconomic analyses support the concept that iNO is a cost-effective intervention, but additional data obtained within the framework of clinical practice are needed. Recent changes in the charge-back arrangements to allow for hourly use of INOmax[®] in multiple patients may relieve some of the budgetary pressure on hospital pharmacies and respiratory therapy departments.

RECOMMENDATION

The Council on Scientific Affairs recommends that:

1. Resolution 417 (I-00) not be adopted.
2. The remainder of this report be filed.

(References pertaining to Report 2 of the Council on Scientific Affairs are available from the Group Office on Science, Quality and Public Health.)

3. GENDER VERIFICATION OF FEMALE OLYMPIC ATHLETES

HOUSE ACTION: RECOMMENDATION ADOPTED AND REMAINDER OF REPORT FILED

INTRODUCTION

Beginning with the 1968 Olympic Games and continuing through 1998, the International Olympic Committee (IOC) required on-site gender verification of female athletes via laboratory-based genetic testing. The rationale was to detect male impostors who would have an unfair competitive advantage based on superior size, strength, and speed associated with androgen-enhanced skeletal muscle mass. Additionally, the granting of eligibility certificates served to silence public innuendoes about the sexual identity of competitors. This policy filtered down to non-Olympic competitions, with no guarantee of quality control.

Concerns about the scientific appropriateness of sex chromatin testing (and later polymerase chain reaction [PCR]-based methods) for gender verification were often expressed throughout this time period. In fact, sex chromatin analysis had been discarded as a common diagnostic tool by geneticists by the 1970s. Several medical and professional societies endorsed resolutions or adopted policy statements in the 1980s and 1990s calling for the elimination of gender verification, including the American Medical Association, American Academy of Pediatrics, American College of Physicians, The Endocrine Society, American Society of Human Genetics, and the Canadian and Australian genetic societies.

In 1998, the IOC's Athlete's Commission called for discontinuation of the laboratory-based system for mandatory gender verification of female athletes. In the summer of 1999, the IOC *conditionally* rescinded its 30-year requirement for on-site gender screening of all women entered in female-only events at the Olympic Games, starting with the Sydney Games in the year 2000. Rather, intervention and evaluation of individual athletes by appropriate medical personnel could be employed if there was any question about gender identity.

This report briefly discusses normal and abnormal sexual differentiation, reviews the history of gender verification requirements for world-class female athletes, and recommends changes in current AMA policy to reflect recent developments in this area.

METHODS

Literature searches were conducted in the MEDLINE database for articles published between 1966 and September 2001 using the search terms "chromatin," "chromosomes," "female," "history of medicine," "sex determination (analysis)," "sex factors," and "sports." Articles were selected that provided historical data and scientific perspective on this issue. Standard medical reference books were consulted for information on sexual differentiation.

CURRENT AMA POLICY

AMA Policy H-470.969 (AMA Policy Database) opposes the continued use of laboratory testing for genetic sex as a basis for verification of gender in athletic competition. When this policy was adopted in 1992, it also called for the IOC to discontinue gender verification, and replace it with a complete medical examination of all athletes, prior to the 1994 Winter Games in Lillehammer, Norway, and the 1996 Summer Games in Atlanta, Georgia.

NORMAL SEXUAL DIFFERENTIATION

Sexual differentiation begins with the chromosomal sex assignment, the heterogamete (XY) being male and the homogamete (XX) being female. Embryos of both sexes develop similarly for approximately the first 40 days of gestation, at which point the uncommitted gonad begins differentiating into a testis or ovary. Presence of a Y chromosome triggers testis development. Differentiation is initiated by actions of the *SRY* gene, a single gene on the short arm of the Y chromosome; however, several other genes are necessary for normal testicular development and regression of the female primordia. It is unclear whether there are analogous "ovarian-determining" genes, or if ovarian development is a default pathway in the absence of testicular development.

The male or female urogenital tracts and external genitalia are formed from the wolffian and müllerian ducts, respectively, based on the type of gonad formed and hormones secreted from the fetal gonads. Formation of the male phenotype is based on the action of two hormones secreted by the fetal testis, antimüllerian hormone and testosterone. After secretion, testosterone undergoes further conversion to dihydrotestosterone, which promotes development of the male urethra, prostate, penis, and scrotum through actions on typical androgen receptors. In the absence of the testes (or androgen secretion) the female phenotype emerges. Normally, phenotypic sex conforms to chromosomal sex, but there are several conditions in which this is not the case. Disorders of sexual development may be chromosomal, gonadal, or phenotypic in origin.

Disorders of chromosomal sex

These occur when the number or structure of the X- or Y-chromosomes is abnormal as in (rare) true hermaphroditism (46,XX or 46,XY or mosaics); Klinefelter syndrome (47,XXY or 46,XY/47,XXY); XX males (46,XX); Turner syndrome (45,X or 46,XX/45,X); and mixed gonadal dysgenesis (46,XY/45,X or 46,XY). The latter is the second most common cause of ambiguous genitalia in the newborn. Mosaicism for a Y-bearing cell line is responsible for most instances. Affected individuals usually have a testis on one side and a streak gonad on the other. The phenotype varies depending on the proportion of XY cells and their distribution. Approximately 60% of these individuals are raised as females.

Disorders of gonadal sex

These occur when chromosomal sex is normal but differentiation of the gonads is abnormal, resulting in conditions in which gonadal sex does not correspond to chromosomal sex.

Pure gonadal dysgenesis is a disorder in which phenotypic females have gonads and genitalia characteristic of gonadal dysgenesis (ie, bilateral streaks, infantile uterus and fallopian tubes, and sexual infantilism) but they attain normal height and have few if any somatic abnormalities. Either a 46,XX or 46,XY karyotype may be present. Individuals with XY gonadal dysgenesis have normal female internal and external genitalia that fail to mature at puberty because only thin streaks of ovarian tissues are present, which are unable to secrete sufficient estrogen to promote development of secondary sex characteristics. Both XX and XY varieties can result from single mutations that are presumed to involve genes essential for gonadal development. About 15% of 46,XY women have either a deletion or a mutation in the SRY coding sequence. Others could have mutations in SRY outside the coding sequence.

Disorders of phenotypic sex

These disorders (pseudohermaphroditism) occur in 46,XX or 46,XY individuals with appropriate gonadal sex but in whom development of the urogenital tract is inappropriate for the chromosomal and/or gonadal sex. Female pseudohermaphroditism occurs in 46,XX women with bilateral ovaries but with variable virilization of the urogenital tract because of androgen excess during fetal life. This may be associated with congenital adrenal hyperplasia (most commonly 21-hydroxylase deficiency), developmental disorders of müllerian ducts, or other nonadrenal enzymatic deficiencies.

Male pseudohermaphroditism is caused by defective virilization of the 46,XY embryo and can result from defects in androgen synthesis, androgen receptors, or müllerian duct regression. Impaired testosterone synthesis accounts for approximately 20% of cases. Defects in androgen action associated either with steroid 5- α -reductase deficiency or receptor disorders are most common. Individuals with androgen insensitivity syndrome are genetically male because they possess both an X and Y chromosome, but their tissues cannot respond to androgens and they develop phenotypically as (sterile) women. The syndrome is caused by mutations of the androgen receptor gene carried on the X chromosome. These XY females are taller than average women. The uterus is absent and the vagina is only one third normal length. Male internal genital ducts remain undeveloped. Normal-sized testes are usually found in the pelvis or at the inguinal ring. Most commonly, androgen insensitivity is complete, but partial sensitivity may be present in about 10% of patients. These individuals exhibit normal patterns of pubic hair and minor virilization of the external genitalia, physiologic changes that offer no competitive advantage.

GENDER VERIFICATION OF WOMEN ATHLETES

The practice of mandatory gender verification of women athletes arose in part because three world champion athletes who competed as women in the 1930s and 1940s (and a World Cup champion skier from the 1960s) subsequently underwent sex reassignment surgery to become males. One individual (Herman Ration) who competed for Germany in the women's high jump in the 1936 Berlin Games (as Dora) later admitted he was a male impostor forced into this role by Nazi Germany. A world-class "female" runner at 400 and 800 meters in the 1960s also was later discovered to be male. Additionally, an autopsy report noted a mosaic sex chromosome pattern and ambiguous sex organs in the 1932 Olympic women's 100-meter sprint champion.

In the 1950s and early 1960s, questions regarding the femininity of highly successful but "masculine" female track and field athletes from the Soviet Union and Eastern Bloc persisted. Coupled with the increasing popularity of women's sports and striking improvement in athletic achievements by women, efforts were made to ensure that women competing at international events were in fact women and that "athletes were competing on an equal basis considering their physical status." Both performance-enhancing drugs and sex impostors were to be prevented by on-site testing.

Gender verification was accomplished prior to international competitions in 1966 and 1967 by physical inspection and/or direct gynecologic examination, a practice that was soon replaced by laboratory-based genetic tests. The IOC officially mandated gender verification for female athletes preceding competition in IOC-sanctioned events beginning in 1968 and continuing through 1998 with laboratory-based genetic tests. From 1968 until 1992, buccal smears were analyzed for the presence of sex chromatin (i.e., inactive X or Barr bodies and fluorescent Y-body chromatin material). The Barr body is formed after inactivation of one of the two X chromosomes in female cells. Many other international and national competitions also adopted this model.

Concerns about the appropriateness of sex chromatin testing for gender verification were voiced continuously in the 1970s and 1980s, but had little impact on IOC governance. These tests detected athletes who were feminine but who happened to have an XY chromosomal pattern, including male pseudohermaphrodites with complete or partial androgen insensitivity and patients with variants of XY gonadal dysgenesis. Sex chromatin tests screened out phenotypic women who had genetic differences that afforded no unusual physical advantage for sports, while potentially missing XX men and women with medical conditions such as congenital adrenal hyperplasia that could offer competitive advantages. At least 13 women were excluded from athletic competition between 1972 and 1990 using sex chromatin testing; many others with abnormal sex chromatin tests "retired" or opted to forgo further assessment to avoid public scrutiny.

Opposing efforts were limited in impact, in part by a lack of information on the frequency of positive results, diagnoses, and follow-up. The tide began turning with the celebrated case of the Spanish national champion hurdler Maria Patino who was disqualified from competing at the 1985 World University Games. Ms. Patino had male pseudohermaphroditism with complete androgen insensitivity. She was the first woman to publicly protest her disqualification and was eventually reinstated. In 1990, the International Amateur Athletics Federation (IAAF) called for an end to required genetic screening of female athletes and in 1992 adopted an approach designed to prevent only male impostors from competing. The IAAF recommended that the "medical delegate" shall have the ultimate authority in all medical matters, including the authority to arrange for the determination of the gender of the competitor if that approach is judged necessary.

The IOC failed to heed this example and beginning in 1992 replaced sex chromatin testing with DNA analysis for Y chromosome material using PCR amplification of chromosomal DNA extracted from nucleated cells. At the 1992 Summer Olympics in Barcelona, 2,406 female athletes were screened for DNA located on the Y chromosome (DYZ1 repeat). Positive samples were reanalyzed for the presence of the *SRY* gene. Eleven were positive for DYZ1; of these, 5 were positive for *SRY*.

The 1996 Summer Games in Atlanta used a comprehensive process for screening, confirmation of testing, and counseling of affected individuals. Eight of 3,387 female athletes had positive test results for *SRY*; 7 had partial or complete androgen insensitivity and the other had undergone gonadectomy and was presumed to have 5- α -reductase deficiency. Two of the seven individuals with androgen insensitivity had not undergone gonadectomy. All of these female athletes were allowed to compete. Overall, the prevalence of male pseudohermaphroditism has been estimated to be 27 in 11,373 or 1 in 421 through five Olympic Games preceding Sydney, compared with an estimated incidence of 1:20,000 to 1:40,000 in the general population.

The shift to PCR-based techniques replaced one diagnostic genetic test with another, but did not alleviate the problems. Positive results still stigmatized women with such conditions as androgen insensitivity, XY mosaicism, and 5- α -reductase deficiency. Both sex chromatin and *SRY* tests identify individuals with genetic anomalies that yield no competitive advantage. Therefore, finally in 1999, the IOC *conditionally* rescinded its 30-year requirement for on-site gender screening of all women entered in female-only events at the Olympic Games, starting with Sydney in 2000. Rather, intervention and evaluation of individual athletes by appropriate medical personnel could be employed if there was any question about gender identity. This change has not been made permanent.

DISCUSSION

Gender verification has long been criticized by geneticists, endocrinologists, and others in the medical community. The combination of invalid screening tests, failure to understand the problems of intersex, the discriminatory singling out of women based only on laboratory results, and the stigmatization and emotional trauma experienced by individuals screened positive prompted organized objection among medical professionals toward gender verification in sports.

Genuine sex-imposters have not been uncovered by laboratory-based genetic testing; however, gender verification procedures have resulted in substantial harm to a number of women athletes born with relatively rare genetic abnormalities affecting gonadal development or the expression of secondary sexual characteristics. The application of this practice is discriminatory and based on a false assumption of unfair advantage. One major problem was unfairly excluding women who had a birth defect involving gonads and external genitalia (i.e., male pseudohermaphroditism) but who had partial or complete androgen insensitivity. Additionally, these tests fail to exclude all potential impostors (e.g., 46,XX males). Individuals with sex-related genetic abnormalities raised as females have no unfair physical advantage and should not be excluded or stigmatized, including those with 5- α -steroid-reductase deficiency, partial or complete androgen insensitivity, and chromosomal mosaicism.

No men posing as women have been detected at the Olympics or other international events at which X chromatin analysis or *SRY* testing has been performed; therefore, gender screening based on finding Y chromosomal material should be abandoned. Of interest, however, is the apparent high frequency of male pseudohermaphroditism in elite class female athletes. The presence of Y chromosomal material is associated with increased height in these athletes. Mean heights are 175 cm or about 69 inches, which is 10 cm taller than normal female controls and only 2 cm less than normal male controls. While some assume that this anomaly may provide potential physical advantages, none of the characteristics, including increased height, are outside of the normal traits exhibited by genetically typical (46, XX) females.

Finally, the current practice of urine testing to exclude doping requires that voiding be observed by an official to verify that a sample from a given athlete has actually come from his or her urethra. Such a practice, performed according to uniform standards, would seem to obviate the possibility of male impostors successfully competing and winning. The new policy advocated by the IAAF and conditionally adopted by the IOC protects rights and privacy for athletes while safeguarding fairness of competition and should become the permanent approach.

RECOMMENDATION

The Council on Scientific Affairs recommends that the following statement be adopted and the remainder of this report be filed:

That American Medical Association Policy H-470.969 be amended by insertion and deletion to read as follows:

Our AMA (1) declares its opposition to the ~~continued~~ use of laboratory testing for genetic sex as a basis for verification of gender in athletic competition, and ~~that gender verification tests be replaced by a complete medical examination for the health and well being of all athletes;~~ and (2) urges the International Olympic Committee to make permanent the 1999 conditional ban on this practice for all future competitions. ~~discontinue gender verification, and to replace it with a complete medical examination of all athletes, prior to the 1994 Winter Games in Lillehammer, Norway and the 1996 Summer Games in Atlanta, Georgia.~~

(References pertaining to Report 3 of the Council on Scientific Affairs are available from the Group Office on Science, Quality and Public Health.)

4. NEWBORN SCREENING: CHALLENGES FOR THE COMING DECADE

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTIONS 501 AND 502 (I-00) AND REMAINDER OF REPORT FILED

Resolution 501 (I-00), introduced by the Medical Student Section and referred to the Board of Trustees, asks:

That our American Medical Association promote the undertaking of pilot state-based demonstration programs for newborn screening of cystic fibrosis (CF) to further clarify issues such as testing methods, cost, adequacy of education/counseling, and risk/benefit to individuals and their families; and encourage states choosing to undertake pilot demonstration programs for newborn screening of CF to coordinate their efforts with other states undertaking similar newborn screening programs.

Resolution 502 (I-00), introduced by the Medical Student Section and referred to the Board of Trustees, asks:

That our AMA, in conjunction with the American Academy of Pediatrics (AAP) and other concerned organizations, study the issue of newborn screening of hereditary metabolic and genetic disorders, and develop recommendations for continuous improvement of newborn screening programs; and work with the AAP and other concerned organizations, especially state and county medical societies, to promote the continuous improvement of newborn screening programs based on recommendations from studies by the AMA, AAP, and other concerned organizations on newborn screening.

METHODS

A literature review was performed using the MEDLINE database for 1993 to 1999 on the terms "newborn screening," "newborn screening" in combination with "cystic fibrosis," and "genetic testing." Genetics laboratories and research scientists were contacted about current newborn screening protocols. In addition, the report reflects discussions with representatives of industry and specialty societies, as well as review of the recent Newborn Screening Task Force Report, "Serving the Family from Birth to the Medical Home. A Report from the Newborn Screening Task Force Convened in Washington, DC, May 10-11, 1999." The goal of the Task Force was to review issues and challenges for the nation's newborn screening programs. A central theme was the wide variation in newborn screening among states. The Task Force report also examines the issue of adding comprehensive CF screening, as well as other screening tests to the panel of diseases that are currently targeted.

BACKGROUND

In the United States, the birth location determines which screening tests are performed on blood samples obtained from newborns. If a child is born in Utah, four tests (for phenylketonuria [PKU], congenital hypothyroidism, galactosemia, and sickle cell anemia) are performed. If the child is born in Wisconsin, screening for 21 diseases is mandated. This report addresses the origins and reasons for such disparities.

In the United States, newborn screening is defined as a public health program designed to identify conditions at an early enough time in life to intervene successfully and reduce (and ideally eliminate) risk for associated disability and mortality.

Approximately 4 million infants are born each year in the United States. Newborn screening has historically been a cost-effective intervention; a number of diseases are efficiently screened for, including PKU, congenital hypothyroidism, galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, sickle cell disease, congenital adrenal hyperplasia, toxoplasmosis, CF, tyrosinemia, HIV infection, medium-chain acyl-coenzyme A dehydrogenase deficiency, and glucose-6-phosphate dehydrogenase deficiency. The approach to newborn screening is based on criteria that have been developed over the last 39 years. These criteria include specific steps: the sample must be collected, and then tested in a standardized laboratory; patient follow-up, including diagnosis and timely treatment is required; and all steps are followed closely by tracking outcomes to validate the system.

The justification for newborn screening is based on the founding principles of screening, which are that the test be accessible, available, economically justifiable, and beneficial, not just for the affected person, but for the family and society as a whole.

HISTORY OF NEWBORN SCREENING

Newborn screening began in the 1960s when Dr. Robert Guthrie developed a screening test for PKU, including the means by which the samples would be collected and transported. PKU is the hallmark screening process and is one of only two diseases that are screened for in most states. Most states mandated PKU screening before the end of the 1960s. This led to federal legislation in 1976 to support screening in order to prevent large disparities in quality across states, as well as to promote the initiation of sickle cell anemia screening nationwide. By 1980, 34 state genetic service programs received federal funding. During the 1980s the infrastructure was improved to facilitate economies of scale. Our AMA opposed government-mandated testing in the early years on the grounds that it intruded on the patient-physician relationship.

Due to the difficulties of coordinating such an extensive undertaking, the Council of Regional Networks for Genetic Services (CORN) was established. The Network initiated guidelines for each center to follow in developing its own system of screening newborns in each state. The next logical step was to ensure the continuous survival of the state-run programs by creating a revenue stream. By 1985, 12 states had developed a payment plan. It should be noted that, in most cases, this revenue does not affect the future care of the patient, but is designed to foster the continuation of the newborn screening program.

Currently, the most useful resource is the National Newborn Screening and Genetics Resource Center (NNSGRC), located in Austin, Texas, which is a federally funded, cooperative program of the Maternal and Child Health Bureau - Genetic Services Branch and the University of Texas Health Science Center at San Antonio - Department of Pediatrics. The mission of the NNSGRC is to provide information and resources on newborn screening and genetics to assist health care professionals, the public health community, consumers, and government officials.

Four reports generated in the past 25 years have strongly influenced and shaped newborn screening. The National Academy of Sciences (NAS) was the first report, followed by the Institute of Medicine (IOM) in 1994, and the Task Force on Genetic Medicine in 1995. The most recent report (1999) is from the Newborn Screening Task Force.

- The NAS Report, “Genetic Screening: Programs, Principles and Research,” created guidelines that specifically examine evidence of substantial public benefit to the patient, family, and health care provider. Feasibility is questioned, and the importance of satisfactory testing methods, availability of appropriate laboratory facilities, and quality assurance are emphasized. Follow-up resources (including education, treatment, and counseling) and acceptable costs-per-unit-test are discussed.
- The IOM report, “Assessing Genetic Risks: Implications for Health and Social Policy,” went further in delineating when to screen for a particular disorder by establishing that there must be a clear benefit to the newborn, and treatment and follow-up must be available. The question of timing of screens was raised; there are some conditions in which outcomes are similar if treatment is begun either before or after symptoms manifest. Another issue raised was whether screening alone was beneficial even if no therapy or treatments were offered. Without treatments for particular screened diseases, the newborn patient (and family) was in the predicament of finding the funds to cover the therapy; hence, follow-up through education and effective treatment is essential if screening is to benefit society. Thus, ethical and social issues began to be raised.
- The Report from the Task Force on Genetic Testing, “Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing,” examined the analytical validity and clinical utility of genetic tests in general. This report concluded that safety and effectiveness of treatments were crucial to the patient after screening was implemented. Informed consent was deemed unnecessary in these cases.
- The Newborn Screening Task Force, “Serving the Family From Birth to the Medical Home,” enhances and clarifies definitions. Clearly, not all medical conditions should be screened for in the newborn period. Criteria for inclusion should include frequency of the condition, effective treatment at an early age, wide accessibility, and safety and precision of the tests. Additionally, a “medical home” should be available, which is defined as a place that is linked to the well being of the individual being screened and a convening point for the individual, family, and health care provider. The informed consent model is altered, giving parents the right to be informed in order to decline the testing, at the potential peril of the individual newborn; hence, the term “mandate” disappeared. Further issues include the need for all state newborn screening systems to be technologically and scientifically current, and the need for uniformity among states. Complex issues such as what to do with the residual blood samples (whether to discard or use in future research) are also discussed.

NEW CHALLENGES FACING NEWBORN SCREENING

The issues noted above arise because the ability to screen for many more disorders has greatly increased, based on new technology, such as the recent introduction of tandem mass spectrometry and DNA-based testing. Another new challenge is managing the flow of information that is accumulating at an ever-increasing rate. If we can gain more information by screening, does that mean that we always should? And if so, how do we manage this information? How does this impact the knowledge about a newborn in terms of pre-symptomatic diseases and well being? How can these technological innovations best be used to improve the health of American children? For example, the March of Dimes supports testing all newborns for a limited number of defined disorders, as these fit the standard criteria of diagnosable, medically treatable disorders for which rapid diagnosis and safe treatment of the newborn are likely to reduce risks of death and/or disability.

NEWBORN SCREENING INFRASTRUCTURE

The primary objective of a state's newborn screening program is to ensure that every newborn receives the available screening services, whether that means offering screening for four or 21 diseases. Newborn screening has been associated with the public health sector since its inception in the PKU-era of the early 1960s. Recently, questions have arisen as to whether the public health agency role in newborn screening should change.

State laboratories are coming under increasing pressure from the private sector. For example, Pennsylvania has outsourced all newborn screening to one laboratory, which now also offers an additional screening panel at extra cost (not covered by most third-party payers). Although widespread outsourcing would rid the system of some problems, such as non-uniform screening for different conditions among states, it may cause other problems. In particular, local efforts to educate health care professionals and the public about newborn screening may suffer. Furthermore, competition for contracts may have negative effects on quality; for example, the oversight of sample collection and follow-up patient services (which are typically funded by the contracted laboratory) may be compromised.

The differences between state laboratories are not always based on peer-reviewed epidemiological studies. Nor is the utility and validity of tests cross-referenced to different state laboratories. In many states, policymakers may not be science literate, and may make decisions based on economic rather than scientific factors. Thus, variability exists between laboratories and, therefore, between states.

These differences reveal the need for more conformity and suggest that standardization through national policy creation may be beneficial. The differences also indicate the need for development of systems architecture to facilitate the storage and dissemination of information, and the eventual creation of comprehensive databases. Questions remain on how to achieve this. How could a national minimum set of newborn screening tests be developed? Would states with more tests (e.g., Wisconsin) drop some low prevalence tests, and states such as Utah (with only four tests offered currently) add more tests to arrive at uniformity?

The central issue is deciding which tests to include in a national screening panel. Several states now have legislation that prohibits removal of a test from the state's panel. CORN has developed guidelines for newborn screening systems; these guidelines include demonstrating value for the affected patient, funding infrastructure, cost utility, and evaluation. To ensure that changes are beneficial, they must be geared toward improving the quality of the newborn screening program. Registry and data programs exist that collect information electronically. Among them are vital registration and the creation of birth certificates, immunization registries, and birth defects registries. The National Vaccine Advisory Committee (NVAC) has developed a system to link to the electronic birth certificates database. If successful, systems that link data sets such as immunization and birth registries can minimize duplication of effort and save valuable resources for such needed services as follow-up for infants who test positive and therapy and treatments. The questions that must be addressed when electing to integrate programs include: Are resources saved? Will there be improvement in the short-run and long-term? Do the clients (i.e., the children and the families) benefit? Is privacy and confidentiality assured? Is there an overall improvement in the health of the child who is tested? Pilot studies must be undertaken to gather data to determine if the programs would be improved if integrated.

ECONOMICS OF SCREENING

A 1988 report issued by the US Congress Office of Technology Assessment (OTA) concluded that a net health care savings of \$3.2 million occurred for every 100,000 infants screened, and a net health care savings of \$93,000 was realized for every case detected and treated. This study examined PKU and congenital hypothyroidism screening and focused only on the incremental costs associated with collection and testing of the first blood specimen (i.e., a fraction of positive cases may be missed if only a single specimen is analyzed during the first few hours after birth). The OTA study also reported on an expanded scenario involving 6 additional screens. However, these additional tests varied in different states; hence, the results are not uniform throughout the United States. The OTA summary indicated that more babies would be saved from deadly diseases, but that the cost would be high.

This raises the issue of measuring costs against benefits. Clearly, screening is intended to prevent disease and the consequences of disease, with the benefits outweighing the initial costs. The possibility that screening may increase the cost of a public program does exist. Health policy analysts measure the cost-to-benefit ratios either by cost-benefit calculations (which place value on everything in terms of US dollars) or by cost-effectiveness (which measures the cost of giving care, versus not giving care) calculations.

Every state has a different method of appropriating funds. Most states help finance their programs with a fee, ranging from approximately \$15 in states offering fewer tests, to \$60 in states offering more tests. While additional tests increase fees substantially per patient sample, the cost-per-disorder-tested is decreasing due to new technology such as tandem mass spectrometry and innovative DNA testing methods. Nevertheless, the high costs of newborn screening, which are likely to increase, may cause financial hardships for some families given the current reimbursement climate.

ADDING NEW TESTS TO AN EXISTING PANEL: CYSTIC FIBROSIS AND THE NEW TECHNOLOGY OF TANDEM MASS SPECTROMETRY

As innovative technology allows early detection of many disorders (common and rare), screening panels have increased in size. Since the original criterion for screening was developed for PKU*, several conditions are now tested for that do not fit into the original paradigm. Several diseases that have no cure and that may be considered fairly rare are screened for in some states. Some other conditions that are detectable are not screened for in every state, due to different state laws, regulations, populations, and other factors. An issue of great importance is tandem mass spectrometry and its ability to test many more diseases at a greatly decreased cost-per-disorder-tested.

Cystic Fibrosis Newborn Screening: Preliminary Results

Cystic fibrosis is an autosomal recessive disorder that affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and the exocrine sweat glands, resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF. Meconium ileus occurs in 10% to 20% of newborns diagnosed with CF. Pancreatic insufficiency with malabsorption occurs in the great majority of patients with CF. Most commonly, the diagnosis of CF is established in individuals long after the newborn period. Patients present with one or more characteristic phenotypic features of CF: presence of 2 disease-causing mutations in the *CFTR* gene, or 2 abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60mEq/L), or an abnormal value for the transepithelial nasal potential difference (NPD). Using the panel of 25 alleles recommended by the American College of Medical Genetics, the *CFTR* mutation detection rate varies with ethnic background.

The incidences are 1 in 2,000 in northern Europeans, 1 in 17,000 in African Americans, and 1 in 9,000 in Hispanics. Seventy percent of the mutations found in northern Europeans have a deltaF508 deletion. However, there are now more than 500 known mutations. The median life expectancy for CF patients is now more than 30 years, and it is projected that in newborn infants it will exceed 40 years.

With regard to improving life expectancy and quality of life, screening for CF at the newborn stage can increase the weight, strength, and nutritional intake of affected individuals, therefore decreasing the long-term hospital care required during the early stages of life. Current research indicates that malnutrition associated with CF can be

* (i) the disorder has a relatively high incidence so that the cost per diagnosed individual is reasonable; (ii) an effective and not overly expensive medical treatment is available; (iii) a relatively inexpensive screening test is available that is suitable for high volume testing (ie, preferable automated); and (iv) the screening test has a high sensitivity (low false-negatives), and high specificity (low false-positives).

prevented by neonatal screening. This, together with the likelihood that interventions used to treat the respiratory component are at least somewhat effective, suggests that the benefits of screening for CF outweigh the costs and risks.

Currently, eight states offer screening for CF: Colorado, New Jersey, Wisconsin, and Wyoming mandate testing, and Connecticut, Massachusetts, Montana, and Pennsylvania offer supplemental or pilot CF newborn screening. The cost of screening a patient for CF is between \$5 and \$6 depending on where the screen is performed. This cost will fall dramatically within the next few years as more innovative and automated procedures are developed and become the norm.

Newborn Screening by Tandem Mass Spectrometry

The use of tandem mass spectrometry has the ability to alter the future of newborn screening in terms of sensitivity, specificity, and scope. This technology will have a significant effect on the criteria for screening. The methodology simplifies sample preparation and eliminates time-consuming preparation techniques. Automated features enhance the equipment's specificity. The end result is that specific, targeted molecular ions from amino acids are first separated, detected, and then quantified. Several methods for newborn screening have been developed since the inception of tandem mass spectrometry in the early 1990s for conditions such as PKU, tyrosemia, maple syrup urine disease, and others.

Since its early success, other analytes have been isolated and measured using tandem mass spectrometry. Acrycarnitines, which are diagnostic for inherited fatty acid oxidation disorders and organic acidurias, can be detected. The most common metabolic disorder screened for is medium-chain acyl-CoA dehydrogenase deficiency, which has a frequency in Pennsylvania neonates of 1 in 8,930. The frequency of specific disorders affects the possibility that screening will be cost-effective. By aggregating several disorders, this value can become more favorable. For example, an aggregate frequency of 1 in 3,445 is obtained by taking into account PKU, hyperphenylalaninemia, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease, glutaric acidemia type I, 3-methylcrotonyl-CoA lysase acidemia, and 3-hydroxy-3-methylglutaryl-CoA lysase deficiency.

Currently, the capital costs of providing the machinery and of providing follow-up services are high. However, these costs are somewhat offset by the automated features and the knowledge obtained with this technique, which will be useful in creating new and improved therapy. However, establishing adequate funding to support these new services for each state program will take time.

CURRENT GOVERNMENT PROJECTS

The Health Resources and Services Administration (HRSA) currently has a 4-year contract with the University of California at Los Angeles to examine, review, and evaluate, in partnership with three states, policies and procedures for informed consent. The program will also examine the use of and storage of residual newborn screening specimens. After evaluation, it will recommend best practices or model policies and procedures that will be pilot-tested in the three partnering states.

As this report was being prepared, the HRSA revealed plans to award the American College of Medical Genetics (ACMG) a 2-year contract to outline a process of standardization of outcomes and guidelines for state newborn screening programs and to define responsibilities for collecting and evaluating outcome data. This will include recommendations for a uniform panel of conditions to include in state newborn screening programs. It is expected that the analytical endeavor and subsequent recommendations will be definitive. The recommendations will be based on best scientific evidence and analysis of that evidence.

CONCLUSION

In summary, newborn screening is a well-developed system that has well-recognized issues that are being addressed by government-mandated groups. Lessons learned at the state level should be applied to create national criteria for newborn screening. This will take time and resources. It is recognized by the major stakeholders that there are clear benefits to this approach, including cost-effectiveness and public health benefits. An entire information technology architecture may need to be developed to achieve this.

Adding additional tests to existing panels is happening quickly. However, deciding which tests to include in a national screening panel is difficult. Several states now have legislation that prohibits removal of a test from the state's panel once it is placed on that panel. Cystic fibrosis is not yet established as a disease to be screened for on a national level, but is one of many diseases that are more regularly screened for in various states. The technology of tandem mass spectrometry is allowing cost-effective screening of many disorders, which has caused a reexamination of the current criteria for screening.

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following statements be adopted in lieu of Resolutions 501 and 502 (I-00), and that the remainder of this report be filed:

That our American Medical Association:

1. Support the report from the Newborn Screening Task Force, "Serving the Family from Birth to the Medical Home. A Report from the Newborn Screening Task Force," and recognize the authors of this report as the major stakeholders in the field of newborn screening.
2. Support the Health Resources and Services Administration, Centers for Disease Control and Prevention, and the American College of Medical Genetics as they study the process of standardization of outcomes and guidelines for state newborn screening programs.
3. Monitor developments in newborn screening and revisit the topic as necessary.

(References pertaining to Report 4 of the Council on Scientific Affairs are available from the Group Office on Science, Quality and Public Health.)

5. SAFETY OF TISSUES FOR TRANSPLANTATION (RESOLUTION 508, I-00)

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTION 508 (I-00) AND REMAINDER OF REPORT FILED

Resolution 508, introduced by the Pennsylvania Delegation at the 2000 Interim Meeting and referred to the Board of Trustees, asks our American Medical Association to:

Encourage the United Network for Organ Sharing or other appropriate organizations to study the benefits of encouraging that tissue procurement and processing agencies strive to become registered by, and embrace the standards of, the American Association of Tissue Banks;

Encourage the National Institutes of Health and other appropriate federal and research organizations to study the risks of adverse events arising in the population of recipients of tissue donation, and that the risks be more thoroughly explored in a broad-based manner with emphasis upon identifying transmission of infectious and other diseases, such as malignancy; and

Encourage the study of the feasibility of autopsy of tissue donors as one significant benchmark for clarifying the presence of potentially transmissible disease.

This report presents information on the role of autopsy in tissue transplantation, the estimated magnitude of the problem of transmissible disease in tissue transplantation, and the FDA's proposed revised external oversight system for tissue transplantation. For the purposes of this report, "tissues" refers to ligaments, dura mater, skin, bone, heart valves, corneas, blood hematopoietic stem cells, manipulated autologous chondrocytes, and spermatozoa originating from live and cadaveric donors.

METHODS

Sources include extensive review of relevant reports from federal offices and agencies, including the Food and Drug Administration (FDA), the FDA's Center for Biologics Evaluation and Research (CBER), and the Office of Inspector General. Particular attention was given to the FDA's Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement. The report also reflects the input of the American Association of Tissue Banks' recently published Standards for Tissue Banks. In addition, MEDLINE was searched using the terms "tissue," "tissue bank," and "transmissible disease."

RISK OF TRANSMISSIBLE DISEASE

The uses of human tissue range from heart valve replacements to corneal transplants. For 1999, the last year for which numbers exist, more than 750,000 tissue allografts were distributed for transplants. These were derived from donations from more than 20,000 donors. Given the exponential increase in tissue transplantation, the risk of transmissible disease from donor tissue has been recognized as a significant problem.

In 1994, in an autopsy study of 94 donors, four (4%) who satisfied all the criteria for tissue donation were found to have potentially transmissible disease (cardiomyopathy of possible viral etiology, sarcoidosis, renal cell carcinoma, and papillary thyroid carcinoma). The authors of this study recommended that routine autopsies be performed on all tissue donors; however, it should be noted that this was a limited study, and in larger studies the risk could be higher or lower. It is unlikely that papillary carcinoma of the thyroid or sarcoidosis would be transmitted through organ or tissue donation of noninvolved organs. Burgess et al. also recognize that a requirement for autopsy could have a negative impact on the altruism of donor families. Logistically, the delay in making histologic diagnosis may jeopardize the viability of certain tissues for transplant. The cost of autopsy is another obstacle, especially as pathology departments may not be sufficiently reimbursed. Current recommendations of the College of American Pathologists (CAP) conclude that the risk of disease transmission is very low to theoretical and does not justify routine autopsies of tissue donors (personal communication, David Mongilo, CAP, October 2001).

The individual risk of transmissible disease varies from tissue to tissue. The following is an overview of the magnitude for some of the more common tissue allografts.

Corneas

More than 7000 corneal transplant are performed each year. Current practice, recommended by the Eye Bank Association of America (EBAA), requires negative test results for HIV 1 and 2, hepatitis B surface antigen (HbsAg), and hepatitis C virus (HCV). Other tests that are commonly done include anti-HBC, syphilis, cytomegalovirus, and human T-cell lymphotropic virus (HTLV) I and II. The value of serologic screening has been demonstrated by Armstrong et al. in a report that examined the prevalence of positive hepatitis B (HBV), HCV, and HIV serology in cornea donors prescreened by medical and social history in Ontario, Canada. The prevalence of positive HBV tests was higher than in a similarly screened cohort of blood donors.

Others have studied the risk of central nervous system (CNS) disease transmission with corneal transplants. Given the incidence of Creutzfeldt-Jakob disease (CJD) in the general population in the United States each year, Kennedy et al. estimate that only 1.3 of more than 45,000 cornea donors would be expected to be affected. Rather than screening for CJD, it is recommended that any donors be excluded as cornea donors who undergo brain autopsy for evaluation of possible CNS disease and that medical history screening be improved.

Rabies has been reported to be transmissible through corneal transplant; however, serology provides effective screening.

Bone

Nearly 40,000 bone allografts are transplanted each year. The rate of infection for allografts has been reported in one series to be as high as 12.2% for allografts (versus 3.5% for autografts). The sources of infection include donor infection, contamination from processing, and a number of recipient factors. The outcome for infection in bone allografts is poor, with the majority of patients requiring amputation or resection for control of infection. The incidence of disease transmission has been significantly reduced by thorough screening protocols. Khan et al. reduced the rate of disease transmission to zero and significantly reduced the rate of infection by screening of bone

donors with a full medical and social history and a panel of serology testing for HBV and HCV, *Treponema pallidum* (syphilis), and HIV. Live donors are re-tested for HIV 90 days after donation, during which time the donated bone is quarantined. Bacterial cultures are obtained at the time of donation and the bone is preserved in antibiotic-containing solution for immediate allograft transplantation. For bone tissues that are further processed, frozen, and thawed prior to use, bacterial cultures are repeated.

Skin

Transmission of cytomegalovirus (CMV) and HIV has been reported following skin allografts. Generally, in a healthy recipient, CMV infection is not serious; however, in an immunocompromised patient, significant morbidity can occur (e.g., CMV pneumonitis). Likewise, HIV has been transmitted via skin allograft. The use of detailed medical and social history-taking and medical testing should clearly identify donations at risk. The absolute magnitude of the transmissible disease associated with skin allografts has not been reported.

Heart Valves

Contamination of human cadaveric heart valves with bacteria has been reported to be as high as 50% in those retrieved in open morgues. Typical flora cultured include both gastrointestinal and skin flora. Bacterial contamination is effectively controlled by standard disinfection protocols; however, fungal contamination is not effectively controlled by the addition of anti-fungal agents. More than 60,000 valve replacements are performed annually, and persistent fungal contamination contributes to nearly 200 deaths from fungal endocarditis each year. The American Association of Tissue Banks (AATB) currently recommends discarding such contaminated valves to eliminate a source of morbidity; however, not all tissue banks are registered with the AATB and hence may not comply with its recommendations.

Peripheral Blood Stem Cell and Cord Blood-derived Stem Cells

As the use of peripheral blood stem cells and cord blood-derived stem cell increases (replacing the use of marrow-derived stem cells), there is a significant risk of transmissible infection. Given the typical immunocompromised state of the recipient, the mortality risk is extremely high. Webb et al. reported that 10 (13.7%) of 73 patients who received hematopoietic progenitor cells that were contaminated before cryopreservation or at thawing developed fever or positive blood cultures with 48 hours of transfusion. The actual rate of contamination in other reports varies from zero to 17%, and in this study was less than 3%. No irreversible clinical sequelae were noted.

Reproductive Tissue Products (Sperm, Oocytes)

Improved attention to quality processing, with better preservation of tissues and lower risk of communicable disease, has been proposed to significantly decrease the cost of reproductive therapy. The FDA recommends testing for sexually transmitted diseases, including antibodies for HIV-1, HIV-2, hepatitis B surface antigen, antibodies to hepatitis C and human T-cell lymphotropic virus type 1, and CMV, as well as serologic testing for syphilis, and cultures for *Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*. Quarantining semen donations until a second round of testing for communicable disease is performed prior to release of the semen for use is under consideration. The FDA recommends that screening emphasize review of the medical history and physical examination. Donor suitability is reviewed every two months for those who donate frequently. One exception to positive serology as a contraindication for donation concerns use of reproductive products from sexually intimate partners for artificial reproductive therapy; in these cases, positive serology for HBV and HCV is not an absolute contraindication.

PROPOSED REVISED OVERSIGHT

Given the magnitude of the issue, the FDA has proposed a revised external oversight system for tissue banking. For the purposes of the proposed rule, the FDA defines tissue banks to include entities that are involved in procuring, processing, storing, and distributing tissue.

Currently, oversight is provided by the FDA through CBER, which focuses on the prevention of transmission of communicable disease by requiring donor screening and testing. The authority for CBER to regulate biological products resides in Section 351 of the Public Health Service Act (US Code, Title 42) and in specific sections of the Food, Drug and Cosmetic Act (US Code, Title 21). Limitations of current tissue bank oversight are outlined in a

report of the Office of the Inspector General. One issue is lack of the accurate number of entities and identification of entities engaged in tissue banking; this would be addressed by requiring registration of all such entities. More than 500 different entities are involved, including the 25 tissue and organ recovery members of the Musculoskeletal Transplant Foundation, the 101 donor centers and 114 collection centers listed by the National Bone Marrow Program, the 112 eye banks that are members of the EBAA, and the 65 manufacturers of human cellular- and tissue-based products currently registered with the FDA. In addition, the American Society for Reproductive Medicine estimates that 129 fertility doctors would be subject to the registration and listing requirements.

Accreditation is available through the AATB, which accredits 58 tissue banks, a very small percentage of the entities engaged in tissue banking. New York and Florida are the only states that license and inspect tissue banks, with additional requirements of screening, testing, and reporting of adverse events. These two states also address issues related to tissue procurement processes, labeling standards, and laboratory testing. California, Maryland, and Georgia require tissue banks to be licensed by the state.

The FDA oversight proposals would bring needed standardization and uniformity to the current patchwork of oversight by requiring registration of all tissue banks, expanded screening and testing, and the use of “good tissue practices.” Adherence to good tissue practices by all registered tissue banks will apply to all the steps in recovery, donor screening, and donor testing, and would also cover the processing, storage, labeling, packaging, and distribution of all tissue products. This proposed oversight refers only to tissue products, not to solid organs, which are overseen by the Department of Health and Human Services’ contract to the United Network of Organ Sharing, which manages the organ procurement/transplant network.

As part of its proposed revision of the oversight system, the FDA has issued a guideline for suitability determination for donors of human cellular- and tissue-based products. It calls for all human cellular- or tissue-based products to be quarantined until the donor has been determined to be suitable on the basis of negative or nonreactive test results that demonstrate the donor is free of risk factors and clinical evidence of infection. Donor testing for HIV type 1 and type 2, HBV, HCV, *Treponema pallidum* (syphilis), HTLV I/II, and CMV is recommended, using FDA-licensed, approved or cleared screening tests. HBV testing for the antibody to the surface antigen connotes infectivity more accurately than testing for the core antibody. However, donors who are repeatedly positive for the core antibody would be excluded. Generally, repeat testing for the core antibody connotes immunity. HBV-DNA testing is increasingly being considered as a confirmatory test in questionable cases. For the issue of CJD and dura mater transplants, a full brain autopsy is recommended to look for histological evidence of CJD. Testing by immunochemistry or Western blot for the protease-resistant prion protein (PrP-RES) has not been approved by the FDA and is still considered investigational. However, negative evidence is considered in terms of excluding possible risk of prion disease.

Additional measures called for by the new oversight system proposed by the FDA would require tissue banks to record and report any adverse reactions involving any transmission of disease, or a failure of the tissue product that is fatal or life-threatening and results in significant impairment or surgical intervention. Timely reporting of adverse events to the FDA would permit an opportunity to analyze and identify the source of contamination in the process of tissue banking. Proper labeling of products is a key element of the new oversight proposal, with special emphasis on documentation of the screening and testing results of the tissue as well as the donated nature of the tissue.

These recommendations are organized under a new rule for “good tissue practices.” This is the third part of an FDA proposal for regulating cellular- and tissue-based products. Key components of good tissue practices include establishment of quality-control programs, adequate organizational structure, and adequate personnel to be able to comply with regulatory requirements; establishment of standard operative procedures for all steps in manufacturing; maintenance of the facility, including provision of adequate storage; record keeping and management and maintenance of complaint files; and procedures for tracking the tissue product from donor to recipient, and recipient to donor.

As a corollary to good tissue practices, the importance of informed consent by the donor or the donor family has been noted by the Department of Health and Human Services, which asked the Office of the Inspector General (OIG) to examine issues related to informed consent. Clearly, the issue of trust underlies the quality of the required medical screening. In the case of cadaveric donation, the family is asked questions of an intimate nature about the donor. Without sufficient respect for donors and their families, the quality of the data could be significantly impaired. The OIG report concludes with recommendations to the tissue bank that families be given written materials that provide fuller disclosure about the uses of tissues and the nature of the donation. At a minimum, the

family should receive a copy of the signed consent form, information on how to follow up with the tissue bank if new concerns arise, a full description of the uses to which donated tissue may be put, and a list of other companies and entities with which the tissue bank has relationships.

CONCLUSION

In the interim since the Pennsylvania Delegation introduced Resolution 508 (I-00), the federal government has finalized proposals to bring tissue banking under a cohesive oversight system. In developing the proposed regulations, the FDA has worked closely with the organizations involved, including the AATB whose standards have been recognized previously as industry standards. The proposed regulatory oversight addresses the concerns of the House of Delegates. The issue will be the adequacy of FDA/CBER resources to provide the much needed surveillance. The medical community must continue to be involved in assuring the quality of the tissue supply.

The risk-to-benefit ratio for tissue donation should be viewed as quantitatively different than for solid organs. For the latter, the availability of an organ can be life-saving, whereas in many cases the availability of tissues is life enhancing. Hence, the standard should be higher for assuring the quality and safety of tissues for transplantation.

RELEVANT AMA POLICY

H-370.988 Regulation of Tissue Banking

Our AMA believes that the concerns over safety in tissue retrieval and transplantation might be best addressed by expansion of the intent of Policy H-370.989 which supports state legislation to mandate the licensing, regulation, and certification of human tissue banks.

Therefore, the AMA supports (1) working with the FDA, nationally-recognized tissue banking organizations, and other appropriate organizations to identify circumstances where enhanced standard setting, state regulation, or federal regulation may be necessary; (2) if recommended by these organizations, a uniform state act developed and passed by individual states that would recognize the standards for tissue retrieval and processing established by nationally recognized tissue banking organizations and that would mandate adherence to specific standards as a condition of licensure and certification for tissues banks; (3) working with appropriate national bodies to evaluate the necessity and feasibility of national computerized registers of tissue donors and recipients, using the National Bone Marrow Donor Registry as the prototype; and (4) exploring the advantages and disadvantages that would attend the consolidation of local, diverse tissue banking operations and organ procurement organizations. (BOT Rep. E, I-89; Reaffirmed: Sunset Report, A-00)

H-370.989. State Regulation and Licensing of Human Tissue Banks

The AMA encourages state legislation to mandate the licensing, regulation, and certification of human tissue banks. (Res. 68, I-87; Reaffirmed: Sunset Report, I-97).

E-2.08 Commercial Use of Human Tissue

The rapid growth of the biotechnology industry has resulted in the commercial availability of numerous therapeutic and other products developed from human tissue. Physicians contemplating the commercial use of human tissue should abide by the following guidelines:

- (1) Informed consent must be obtained from patients for the use of organs or tissues in clinical research.
- (2) Potential commercial applications must be disclosed to the patient before a profit is realized on products developed from biological materials.
- (3) Human tissue and its products may not be used for commercial purposes without the informed consent of the patient who provided the original cellular material.
- (4) Profits from the commercial use of human tissue and its products may be shared with patients, in accordance with lawful contractual agreements.
- (5) The diagnostic and therapeutic alternatives offered to patients by their physicians should conform to standards of good medical practice and should not be influenced in any way by the commercial potential of the patient's tissue.

(Issued June 1994 based on the report "Who Should Profit from the Economic Value of Human Tissue? An Ethical Analysis," adopted June 1990.)

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following be adopted in lieu of Resolution 508 (I-00), and that the remainder of this report be filed:

1. That American Medical Association Policy H-370.988 be amended to read:

~~Therefore, the Our AMA (1) supports (1) working with the FDA, the Food and Drug Administration's (FDA) proposed regulatory agenda for tissue banking organizations, and urges the FDA to continue working with nationally-recognized tissue banking organizations, to develop guidelines and implement the proposed oversight system; and other appropriate organizations to identify circumstances where enhanced standard setting, state regulation, or federal regulation may be necessary; (2) if recommended by these organizations, a uniform state act developed and passed by individual states that would recognize will promote the adoption of the standards for tissue retrieval and processing established by nationally recognized tissue banking organizations and that would mandate adherence to specific standards as a condition of licensure and certification for tissues banks; (3) will support FDA registration of all tissue banks, working with appropriate national bodies to evaluate the necessity and feasibility of national computerized registers of tissue donors and recipients, using the National Bone Marrow Donor Registry as the prototype; and (4) exploring the advantages and disadvantages that would attend the consolidation of local, diverse tissue banking operations and organ procurement organizations. (BOT Rep. E, I-89; Reaffirmed: Sunset Report, A-00)~~

2. That AMA Policy H-370.989 be amended to read:

~~The Our AMA encourages state legislation to mandate the licensing, regulation, and certification of human tissue banks states to require licensing of human tissue banks in a manner consistent with the Food and Drug Administration's federal regulatory requirements.~~

3. That our AMA support efforts to ensure that the FDA has adequate resources to carry out the oversight activities outlined in its current proposed rule.
4. That our AMA support the continued involvement of the medical community in the further effort to ensure the safety and efficacy of the nation's supply of tissues.
5. That our AMA continue to promote physician awareness of the need for organ and tissue donation.
6. That our AMA recognize the altruism of the donors and donors' family that makes the availability of tissues a reality for the more than 700,000 recipients of tissue allografts in the United States.

(References pertaining to Report 5 of the Council on Scientific Affairs are available from the Group Office on Science, Quality and Public Health.)

6. IMPLEMENTING THE GUIDES TO COMMUNITY PREVENTIVE SERVICES (RESOLUTION 414, I-00)

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTION 414 (I-00) AND REMAINDER OF REPORT FILED

His [the physician's] relationship was formerly to his patient--at most to his patient's family; and it was almost altogether remedial. The patient had something the matter with him; the doctor was called in to cure it. Payment of a fee ended the transaction. But the physician's function is fast becoming social and preventive, rather than individual and curative. Upon him society relies to ascertain, and through measures essentially educational to enforce, the conditions that prevent disease and make positively for physical and moral well-being.--Abraham Flexner, 1910.

Resolution 414 (I-00), introduced by the American College of Preventive Medicine and referred to the Board of Trustees, asks:

That our American Medical Association establish a process to consider endorsing each set of completed reviews and recommendations associated with the Guide to Community Preventive Services as they are periodically published by the Task Force on Community Preventive Services;

That our AMA, as part of the endorsement process, identify and suggest strategic partnerships (e.g., state/local medical societies, public health agencies, managed care organizations, employer groups, etc.) for implementing the interventions; and

That our AMA publicize (e.g., in its journals and newsletters) the reviews and recommendations, as well as any AMA endorsements, and support the efforts of its Federation partners to implement the recommendations.

RELEVANT AMA POLICY

Our AMA recommends the US Preventive Services Task Force Guide to Clinical Preventive Services (2nd edition) to clinicians and medical educators as one resource for guiding the delivery of clinical preventive services. The Guide should not be construed as AMA policy on screening procedures and should not take the place of clinical judgment and the need for individualizing care with patients (H-410.967, AMA Policy Database).

Prevention should be a philosophy that is espoused and practiced as early as possible in undergraduate medical schools, residency training, and continuing medical education, with heightened emphasis on the theory, value, and implementation of both clinical preventive services and population-based preventive medicine (H-425.984).

It is the policy of our AMA that: (1) physicians should become familiar with and increase their utilization of clinical preventive services protocols; (2) individual physicians as well as organized medicine at all levels should increase communication and cooperation with and support of public health agencies. Physician leadership in advocating for a strong public health infrastructure is particularly important; (3) physicians should promote and offer to serve on local and state advisory boards; (4) physicians and medical societies should advocate for the adoption of local/state health objectives for the year 2000; and (5) in concert with other groups, physicians should study local community needs, define appropriate health objectives, and work toward achieving health goals for the community (H-425.986).

Our AMA will engage in activities, including but not limited to: educating members on Healthy People 2010 through sponsored Continuing Medical Education events and publications; encouraging state medical societies to engage in promoting activities that address the elimination of health disparities; and investigating the development of a partnership with the Department of Health and Human Services to work to accomplish the goal of eliminating disparities on the basis of race and ethnicity (H-350.967).

BACKGROUND

The Task Force on Community Preventive Services (the Task Force) was convened by the Centers for Disease Control and Prevention, US Public Health Service, to identify population-based recommendations (Community Guides) to reduce the risks that contribute to the leading causes of morbidity and premature mortality. The recommendations are intended to complement the Guidelines for Clinical Preventive Services, which were developed and updated by the US Preventive Services Task Force convened by the Agency for Health Quality and Research. Although the Community Guides are primarily intended for use by public health audiences, they will make a major contribution to addressing the spectrum of disease prevention, health policy, and health promotion, including interventions provided within medical settings. The membership of the Task Force is multi-disciplinary, and includes perspectives representative of state and local health departments, managed care, academia, behavioral and social sciences, communications sciences, mental health, epidemiology, quantitative policy analysis, decision and cost-effectiveness analysis, information systems, primary care, and management and policy. Of this group, nine members are physicians.

To understand the rationale for the Community Guides, several working definitions are necessary:

Community - A group of individuals who share one or more characteristics.

Community preventive service - An intervention that prevents disease or injury or promotes health in a group of persons. Interventions are usually either primary, in that they attempt to reduce risk factors that lead to disease or else secondary, in that they contribute to increased early identification of disease. These interventions may include procedures delivered to the entire community, such as mass media campaigns; to groups of individuals in schools or worksheets, such as school health education or workplace wellness programs; and to groups of patients in clinical settings, such as chart reminders to provide immunizations. Interventions may also include mandated health regulations, such as immunization requirements for school entrance.

Clinical preventive services - Screening, counseling, and immunization procedures provided to asymptomatic patients.

Community Preventive Interventions - One or more activities that are characterized by what was done, how it was delivered, who was targeted, and where it was delivered. Interventions can be single-component, using only one activity or multicomponent, using more than one related activity.

The Task Force will review recommendations in 15 evidence-based topic areas. These are clustered into three themes: Changing Risk Behavior, Reducing Specific Injuries, Diseases, and Impairment, and Addressing Environmental and Ecosystem Challenges:

Changing Risk Behaviors

- Tobacco
- Alcohol
- Other Addictive Drugs
- Physical Activity
- Nutrition
- Sexual Behavior

Reducing Specific Injuries, Diseases, and Impairment

- Vaccine Preventable Diseases
- Cancer
- Diabetes
- Improving Pregnancy Outcomes/Infant Mortality and Health
- Depression and Comorbid Factors
- Motor Vehicle Occupant Injury
- Oral Health
- Violent and Abusive Behavior

Addressing Environmental and Ecosystem Challenges

- Sociocultural Environment

The Task Force used the following inclusion criteria when considering topics: (1) the burden of disease, injury, impairment or exposure; (2) preventability; (3) related initiatives such as the Health Plan Employee Data and Information Set (HEDIS) and Healthy People 2010; and (4) usefulness of the set of topics selected to the target audience.

Each topic area contains a series of recommendations. The recommendations consist of one or more of the following preventive interventions:

- strategies to educate the general public (e.g., mass media) or specific populations (e.g., school health education);
- strategies to mandate compliance (e.g., health legislation and regulations);
- strategies that could be used in the clinical setting to increase delivery of preventive interventions (e.g., chart reminders); and
- strategies in health policy designed to improve community health (e.g., increasing excise taxes on tobacco products).

METHODOLOGY OF GUIDELINE DEVELOPMENT

Each chapter of the Community Guides is being developed according to a standard protocol.

1. A multidisciplinary chapter development team is formed that includes four to ten health professionals with methodological or subject matter expertise.
2. A conceptual (e.g., logic) framework is developed that maps out the chain of hypothesized causal relations among determinant, intermediate, and health outcomes. The framework is then used to identify explicitly strategic points for actions and the range of preventive interventions that could be directed at these strategic points. The conceptual framework guides the systematic literature reviews.
3. Interventions for evaluation are identified. Since there are usually a variety of possible interventions for each linkage within each conceptual framework, the chapter teams are basing selections of interventions on:
 - The potential for reducing the burden of disease and injury
 - The potential for increasing healthy behaviors and reducing unhealthy behaviors
 - The potential to increase the implementation of effective interventions that are not widely used
 - The potential to phase out widely used, but less-effective interventions in favor of more effective options
 - The current level of interest among health care providers and decision makers
4. Systematic searches of the scientific literature are conducted that meet the inclusion criteria for specificity of intervention and outcome.
5. The evidence on effectiveness for each intervention is assessed by the methodological quality and results of the studies. Two reviewers from each chapter team evaluate the studies, extract the results, summarize the evidence, and assess the strength of the body of evidence. A standardized abstraction form is used that includes 28 questions on content and 23 questions on the quality of the execution of the study. Using a specific set of criteria, study designs are characterized by suitability (e.g., greatest, moderate, and least) for assessing the specific intervention under question. Reviewers then evaluate the quality of study execution (e.g., good, fair, or limited quality) according to nine limitations. Studies that are evaluated as having limited quality of execution are not used to summarize the body of evidence. Results across a group of related studies are summarized using, when appropriate, quantitative statistical measures to measure variability of data. Finally, “the body of evidence of effectiveness is characterized as strong, sufficient, or insufficient based on the number of studies, the strength of their design and execution, and the size and consistency of report effects.”
6. Recommendations are developed from the summary of the body of evidence. The Task Force uses evidence on effectiveness to make a recommendation basically supporting or not supporting each intervention. A judgment is also provided on how widely each recommendation should be applied, as well as commentary on likely barriers to implementing the intervention.
7. Gaps in research are identified.

PROGRESS TO DATE ON GUIDELINE DEVELOPMENT

As of the end of August 2001 the Task Force had completed sets of recommendations for the following topics:

- Vaccine Preventable Diseases
- Tobacco Use Prevention and Control
- Motor Vehicle Occupant Injury

CONCLUSIONS

It is clear that the Task Force on Community Preventive Services is using a rigorous methodology to develop recommendations for population interventions. It is also clear that these recommendations will be useful to practicing physicians both in their role as direct service providers and their role as advocates within their local communities.

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following be adopted in lieu of Resolution 414 (I-00), and that the remainder of this report be filed:

1. That our American Medical Association commend the Centers for Disease Control and Prevention (CDC) and the Task Force on Community Preventive Services for their work in developing the Guides to Community Preventive Services.
2. That our AMA review the recommendations and conclusions of the Task Force on Community Preventive Services and recommend to the House of Delegates the appropriate actions as per AMA policy.
3. That our AMA express to the Director of CDC our support for the establishment of a working group between the CDC and the AMA and our specialty organizations plan for promoting the implementation of the Guides to Community Preventive Services within the private medical sector.
4. That our AMA promote the visibility of the recommendations of the Guides to Community Preventive Services as they become available, provided those recommendation comport with AMA policies and standards.

(References pertaining to Report 6 of the Council on Scientific Affairs are available from the Group Office on Science, Quality and Public Health.)