Testimony
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CDC Response to Infections Related to Human Tissue Transplantation

Statement of
Steven L. Solomon, M.D.
Acting Director
Division of Healthcare Quality Promotion
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Department of Health and Human Services

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Good morning, Madam Chairwoman and Members of the Committee. I am Dr. Steven L. Solomon, Acting Director of the Division of Healthcare Quality Promotion in the Centers for Disease Control and Prevention's (CDC) National Center for Infectious Diseases. Thank you for the opportunity to report to you on CDC's activities with regard to the problem of infections occurring in association with the surgical implantation of transplanted human tissue.

Introduction

An allograft is human tissue, which is recovered from cadavers and processed before being transplanted into another person. The most common type of allograft is bone. Tendons, skin, heart valves and corneas are other common types of human tissue allografts. Allografts may be life saving and can substantially improve the quality of life for many patients, reducing disability and restoring mobility or sight. The use of allografts has increased dramatically in recent years. In 1999, tissue banks in the United States distributed approximately 650,000 musculoskeletal allografts, compared with 350,000 in 1990.

As with any surgical procedure, the implantation of human tissue allografts may be associated with complications, including infections at the surgical site. Although rare, some of these infections are associated with bacterial contamination of the implanted allografts, a complication that can result in serious morbidity and death. The findings associated with CDC investigations of allograft-associated infections have important implications for patient safety. In collaboration with the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and other partners, CDC continues to investigate reports of infections and assess the need for possible changes in the processing and quality control methods for allografts as a means of

preventing allograft-associated infections.

As indicated, transplanted tissue is commonly obtained from cadaveric material. After recovery from a cadaver, allografts may be processed by either sterilization or aseptic processing without sterilization. In aseptic processing, careful handling ensures that no new organisms are introduced during the recovery of tissues from the cadavers. Tissues may be treated with chemicals or antibiotics to minimize intrinsic contamination, that is, bacteria that contaminate these tissues following death, and prior to or during recovery of the tissues. Thus, the tissue is not sterilized—the processing is only intended to reduce intrinsic contamination and prevent further contamination of the tissue.

Sterile processing involves the use of aseptic techniques during the recovery of tissue followed by treatment of tissue to eliminate contamination with bacteria, and other microorganisms such as mycobacteria, viruses, fungi, and spores. Gamma irradiation and use of ethylene oxide were historically used to sterilize tissues for the presence of microorganisms. Gamma irradiation at high dosages affects the biomechanical properties of the tissue, rendering some tissues nonviable. Although ethylene oxide sterilization does not affect the biomechanical properties of the tendon, it is associated with other complications following transplantation, such as inflamation at the site of implantation. Because of these inherent problems with gamma irradiation and ethylene oxide, most transplanted tissues obtained from cadavers has been processed aseptically rather than sterilized. However, because of the small but finite risk of potentially life-threatening infection from such tissues, new tissue sterilization methods, such as low temperature chemical sterilization, have been developed.

CDC Investigations Summary

In November 2001, CDC began an investigation after receiving a report from the Minnesota Department of Health of a fatal case of infection with *Clostridium sordellii* bacteria in a patient in Minnesota who had recently received a bone-cartilage allograft. A few days after surgery, the patient developed pain in the knee that rapidly progressed to shock; the patient died the following day. The laboratory found *C. sordellii* bacteria in cultures of the patient's blood obtained prior to his death. Investigators at CDC contacted the tissue bank from which the transplanted allograft had been obtained, and the tissue bank provided CDC with samples of non-implanted tissues from the same cadaveric donor. CDC laboratories identified *C. sordellii* in some of these tissues. As a result, CDC concluded that the infection in the patient in Minnesota resulted from intrinsic bacterial contamination of the cadaveric cartilage tissue. CDC subsequently contacted the healthcare providers of all patients who already received transplanted allografts from this same donor to determine if other infections had occurred. CDC found that ten tissues had been transplanted into nine patients located in eight states. One of these patients developed an infection following the surgical procedure. The CDC/FDA investigation showed that intrinsic bacterial contamination was possible because the allografts in this case had been processed aseptically before being sent out from the tissue bank but not sterilized.

In June 2002, CDC was asked to assist in the investigation of an increased rate of post-operative surgical site infections in patients at an outpatient surgery facility in California. CDC determined that the increased rate of infection was associated with patients who underwent specific types of orthopedic procedures in which an allograft implantation was used. Although intrinsic contamination of allografts was not shown to be the only cause of the infections associated with this increased rate of infection, all of the infected

patients had received aseptically, as opposed to sterile, processed allografts—by far the most commonly used procedure. None of the patients who received autografts (transplants of the patient's own tissue) or allografts that had been sterilely processed developed infection.

In addition to investigating infections associated with bacterial contamination of allografts, CDC has investigated reports of infections caused by fungi, parasites, and viruses following transplant of organs and tissues.

Investigations of non-bacterial contamination

Hepatitis C

In June 2002, a physician reported to the Oregon Department of Health Services a case of acute hepatitis C in a patient that had received a patellar tendon with bone allograft from a donor approximately 6 weeks before the onset of his illness. No detectable antibody to hepatitis C virus (anti-HCV) had been found in the donor's serum at the time of his death in October 2000. The ensuing investigation conducted by CDC and Oregon Department of Human Services confirmed that the donor, although antibody negative, was infected with hepatitis C virus (HCV) as determined by positive results of testing for HCV RNA and was the probable source of HCV infection in at least eight recipients of organs or tissues from this donor. Although transmission from anti-HCV negative tissue donors probably is rare, determining the frequency of transplantations from such donors and the risk for transmitting HCV to recipients will be useful for evaluating the benefits and limitations of additional prevention measures such as nucleic acid testing to detect HCV RNA among organ and tissue donors.

West Nile Virus

In August 2002, several recipients of organs from a common donor developed fever with mental status changes. CDC, FDA, the Georgia Department of Public Health, and the Florida Department of Health conducted an investigation. This cluster represents the first recognized transmission of West Nile virus by organ transplantation. Findings from this and concurrent investigations have prompted FDA guidance to the blood industry to reduce the risk of transmitting West Nile virus infection through transfusions. Additionally, FDA is working with the blood and medical diagnostics industry to speed development of West Nile virus screening tests. CDC has strongly encouraged clinicians to report West Nile virus-infected patients who develop symptoms within 4 weeks after receiving organ/tissue transplantation or blood transfusions, or within two weeks after donating blood, organ, or tissue. Prompt reporting of these cases will assist in withdrawal and retrieval of potentially infected tissues and blood products and will help define the epidemiology and clinical significance of West Nile virus-related transmission through transplanted organs and transfused blood.

Chagas Disease

On April 23, 2001, a physician notified CDC of an acute case of Chagas disease. Chagas disease is an infection caused by the parasite *Trypanosoma cruzi*. It is estimated that 16-18 million people are infected with this parasite. In parts of Latin America, of those infected, an estimated 50,000 die each year. Chagas disease following solid-organ transplantation has occurred in Latin America, where Chagas disease is endemic, but had not been reported previously in the United States. This investigation identified three cases in the United States of *T. cruzi* infection associated with transplantation of cadaveric organs from a single donor. The donor, who had previously resided in an area in which Chagas' diseases is endemic, had antibodies to *T. cruzi*, which supported the conclusion that he had been infected with this parasite.

CDC and the scientific committees of the Organ Procurement and Transplantation Network/United Network for Organ Sharing, are reviewing what steps to take with regard to the feasibility of laboratory testing of potential organ donors for *T. cruzi* infection.

Prevention Measures

Prevention of infections from transplanted tissues and organs requires both careful screening of donors and careful adherence to specific guidelines for processing and quality control measures such as culturing tissues before processing. Ultimately, CDC believes that the best way to reduce the risk of transmission of infectious agents associated with tissue transplants is to develop new methods of sterilizing tissue that do not adversely affect the functioning of the tissue when transplanted into patients.

As noted previously, both sterilization methods commonly in use (ethylene oxide and gamma irradiation), although effective even against bacterial spores such as those found in the Minnesota case, have associated technical problems. Nonetheless, the potential risks associated with the transplantation of aseptically processed tissues suggest that existing sterilization technologies used for sterilizing allografts, such as gamma irradiation, or new technologies with increased effectiveness against bacterial spores should be considered whenever possible.

Every effort should be made to use suitable sterilization methods; however, if that is not possible, every effort should be made to minimize the risk of intrinsic bacterial infection. Recovered tissue should be cultured before suspension in antimicrobial solutions, and if bacteria commonly found in the human bowel are isolated, all tissue from that donor that cannot be sterilized should be discarded. Culture methods need to be validated to

ensure that residual antimicrobials in the treatment solution do not result in false negative culture results. Performing both destructive and swab cultures should be considered. Recommended time limits for tissue retrieval should be carefully followed, since the risk of intrinsic bacterial contamination increases the longer the delay between the donor's death and the recovery of the tissue for transplantation. After a tissue bank or tissue processor receives a report of potential allograft-associated infection, remaining tissue from that donor should not be released until it is determined that the allograft is not the source of infection. Tissue processors should promptly contact public health authorities and health-care providers of recipients of tissue from the same donor implicated in an allograft-associated infection. In these cases, a sample of non-implanted tissues from that donor that were processed using the same processing method as the implicated tissues should be cultured by an independent laboratory using a validated method.

Public Health System Responses

Other public health interventions that will greatly facilitate the prevention and control of infections associated with tissue and organ transplantation are enhanced surveillance and enhanced communication with clinicians.

As part of the Minnesota investigation, CDC, in collaboration with FDA, requested that cases of allograft-associated infections be reported to CDC through state and local health departments, in addition to reporting of such cases to FDA. As well, cases reported to FDA were shared with investigators at CDC and state health departments.

As of March 2003, CDC had received reports of 62 allograft-associated infections. Ninety-three percent of these infections were associated with musculoskeletal tissues.

Cases of infection were reported from 20 states and involved tissues that had been treated at 12 different tissue processors. One tissue processor was associated with 45% of all reported infections. These surveillance findings have been shared with the American Association of Tissue Banks, FDA, and others.

Public health surveillance is critical to our ability to improve patient safety by preventing post-surgical complications such as allograft-associated infections. We cannot investigate problems, identify their causes, and implement control measures if we have not detected them. CDC surveillance data come from state and local health departments, as well as directly from healthcare providers and from patients, particularly from patients when a cluster of cases is heavily covered in the media, as in this case.

Although both CDC and FDA do receive reports of post-surgical infections that may be associated with contaminated tissues and organs, both agencies are currently working to enhance their ability to capture this much-needed information. Most reports are received through passive surveillance, which relies on the ability of alert clinicians to recognize a particular problem and their awareness of their role in reporting it to the appropriate public health authority. Passive surveillance systems, while less costly, often provide incomplete information and fail to capture many cases that occur.

By contrast, active surveillance uses a variety of methods to maintain communication with potential reporting sources to increase the completeness and accuracy of surveillance information. Through CDC's ongoing partnership with FDA, and with the cooperation of the tissue banking industry, CDC has continued to receive reports of post surgical complications associated with allograft transplants, some of which appear to be consistent with allograft-associated infections. As indicated earlier, reporting of

allograft-associated infections increased significantly in the period following publication of the *Morbidity and Mortality Weekly Report* article describing the first case in Minnesota. The frequency of reports has declined in recent months; whether this is because fewer cases are occurring or because fewer cases are being reported is a question that can only be answered by active surveillance. CDC has had effective active surveillance systems for monitoring healthcare-associated infections for over thirty years, through systems such as the National Nosocomial Infections Surveillance System. However, these systems have been limited in scope due to the significant burden on reporting sites of maintaining highly standardized and labor-intense detection methods and being assiduous in the completeness of their reporting.

By making use of advances in information technology, CDC is developing a greatly enhanced healthcare-based surveillance system called the National Healthcare Safety Network (NHSN). The NHSN will integrate, expand and improve successful public health knowledge management systems that consist of data analysis, feedback of health care institution-specific data, and linkage of data with guidelines and educational materials for health care providers. By connecting clinicians and other healthcare professionals to FDA and CDC guidance, to information about specific syndromes, such as allograft-associated infections, and to public health authorities, this system is being designed to complement the reporting function and quickly provide prevention and response information to the user.

NHSN is being designed to be a principal means for hospitals and other healthcare-institutions to collect and manage and report patient safety information in collaboration with CDC, other federal agencies, and state and local public health authorities. The NHSN will be a fully integrated component of CDC's Public Health Information Network

and adhere to the standards of CDC's National Electronic Disease Surveillance System.

Conclusion

Addressing the problem of infections associated with blood, tissue and organ receipt is part of the larger problem of patient safety, requiring significant changes throughout all parts of the healthcare industry. Organizations involved in organ and tissue procurement, and suppliers and processors of tissues must put in place assiduously followed procedures to assure that any risks associated with tissue transplantations are greatly minimized if not eliminated. State and federal public health authorities must continue to enhance their ability to collect, analyze, interpret, and disseminate information about potential patient safety hazards due to biological products (including blood, tissue and organs), medical devices, and medical procedures. Clinicians and medical professionals must, with our help, increase their awareness of specific patient safety problems and fulfill their role in reporting such problems promptly to the appropriate authorities so that appropriate action can be taken. CDC, FDA, and other partners, as noted earlier, are actively engaged in ensuring that biological products, including tissue allografts, are as safe as possible.

The recent report by the Institute of Medicine (IOM) entitled, *Microbial Threats to Health: Emergence, Detection, and Response* recognized thirteen individual factors contributing to the emergence of microbial threats. These investigations highlight one of these factors identified by the IOM, "the role of advances in medical technologies, such as blood transfusion and organ transplants, [that] have created new pathways for the spread of certain infections."

Thank you very much for your attention. I will be happy to answer any questions you

may have.