Managing INFECTION CONTROL™
www.manageinfection.com
February 2007
Volume Seven Issue 2

February 2007

Allograft Tissue Sterilization

A discussion of allograft tissue implant sterilization techniques

Resulting from active lifestyles, nearly two million Americans annually undergo orthopedic surgical procedures. With the common use of allograft tissue in these procedures, it is essential that surgeons and medical professionals keep informed of the ever-increasing technology that is making this a safer option in treating patients with musculoskeletal problems.

Managing Infection Control (MIC) recently spoke with Alexander A. Sapega, M.D., a practicing orthopedic surgeon at the New Jersey Knee and Shoulder Center in Mount Laurel, N.J., to gain insight on the issue of allograft tissue implant sterilization. In the following pages, Dr. Sapega shares his thoughts.

MANAGING INFECTION CONTROL: Describe the differences between autografts and allografts. What are the benefits of both tissues?

Dr. Sapega: *Autografts* are surgically harvested tissue specimens obtained from the same patient who is undergoing the surgical procedure in question. Typically, at the time of surgery, one body part or a portion of a body part is used to reconstruct or replace another. Effectively, this is a surgical equivalent of the old adage "robbing Peter to pay Paul." Typically, the tissue specimen that is harvested from one portion of the body is reasonably expendable, and serves a more important role in rebuilding or reconstructing the missing or damaged body part where it will be used. In my surgical specialty, which is arthroscopic and reconstructive knee surgery, surgeons will often harvest a patient's normal hamstring tendon or a portion of their patellar tendon to rebuild a damaged or torn anterior cruciate ligament within the knee joint. In the majority of cases, the loss of function and surgical morbidity associated with the harvesting of the autograft is outweighed by the benefits of a successfully reconstructed anterior cruciate ligament.

An *allograft*, on the other hand, is an otherwise similar tissue specimen that has not been harvested from the patient in question, but from a tissue donor. Ligament and tendon tissues for reconstructive knee surgery are typically procured from deceased tissue donors immediately after these donors have their transplantable organs harvested for donation to an

organ transplant center. The structural tissue quality of the donor is generally equivalent to the tissue quality that would be obtained if the specimen were harvested from the patient him or herself, and the advantage is that the patient does not need to sacrifice any of his or her own healthy tissue in order to rebuild the compromised body part in question. In my opinion, were all other things guaranteed equal, almost all patients would prefer an allograft tissue implant to rebuild a damaged or torn body part over having to sacrifice some of their own healthy tissue to accomplish the same purpose. Those of my patients who have chosen autograft reconstruction of their cruciate ligament, as opposed to allograft reconstruction, have generally done so out of fear of contracting an undetected infectious disease from the tissue donor. This leads to your second question.

MIC: What are some of the risks associated with allograft use?

***Dr. Sapega*:** The principal risk for both patient and surgeon to be concerned about is the unintended transmission of an infectious disease from the tissue donor to the tissue recipient. While statistically, this is a relatively small risk, it is one that is still intimidating, if not frightening, when contemplated by many patients. Despite the many screening and testing procedures typically employed by accredited and certified bone and tissue banks, up until very recently, I had to inform my preoperative patients that if they chose an allograft method of reconstructing their cruciate ligament, I could not positively guarantee them that the tissue I would be implanting into their body would be sterile, and not contaminated with hepatitis C virus, AIDS virus, or some dangerous variety of infectious bacteria. If I did not inform my patients of this risk, no matter how small, I would not be conducting a full and proper informed consent. Toward this end, I developed a written patient consent form concerning allograft tissue implantation, which all of my allograft surgery patients had to read and sign, preoperatively. The text of this informed consent document read as follows:

> *I hereby attest that after discussion with my surgeon, Dr. Sapega, I have elected to have my knee condition treated by surgery that includes the implantation of an "allograft" tissue specimen, obtained from a certified bone and tissue bank. The advantages and disadvantages of allograft tissue implantation versus other available treatment methods have been satisfactorily explained to me by Dr. Sapega. I understand that allograft surgery is well accepted in orthopedic practice today, but I have also been made aware that despite all of the screening and safety procedures employed by bone banks, it still cannot be absolutely, positively guaranteed that my allograft tissue is not contaminated with bacteria that could cause a serious knee or other infection (or even death) or my contracting a potentially fatal viral disease such as AIDS or hepatitis. I understand that one research group has recently (October, 2002) estimated that the rate of allograft contamination with hepatitis virus may be as high as 1 in 2,500, and the rate of contamination with HIV (AIDS) virus may be as high as 1 in 49,000, even in properly screened donor specimens. I have consented to preoperative hepatitis and HIV screening tests for myself to rule out the possibility of any preoperative infection. (Patient signature follows.)*

I had all of my allograft surgery patients tested for hepatitis and AIDS before surgery to make sure that there was no hidden disease present before I operated, which when subsequently detected, might be blamed upon my allograft surgery. The cost and inconvenience of this additional preoperative testing, in

combination with the emotional effect of the "cold hard facts" laid out in my allograft surgical informed consent form, were definite impediments for some of my patients when considering the other advantages of allograft tissue surgery. Some patients were willing to accept this inconvenience and the statistically minute chance of infectious disease transmission, whereas other patients felt they simply did not want to live with the thought of potentially contracting a fatal, or at least serious, infectious disease, no matter how unlikely. However, this past year I began using cruciate ligament tissue implants treated by way of the Clearant process. This has allowed me to offer the effective equivalent of allograft implant sterility to my patients, and has obviated the need for my allograft surgical informed consent form, as well as the preoperative Hepatitis and AIDS screening tests. This has simplified and reduced the stress of the preoperative decision-making process for my patients, and the percentage of my patients who have chosen allograft surgery over autograft surgery has increased dramatically since I have been able to offer them the benefits of the Clearant allograft treatment process.

MIC: Have there been cases of allograft infections in the past?

Dr. Sapega: Yes indeed, although fortunately the number of reported infections has been very small. Over the years, sporadic cases of tragic infectious disease transmission have occurred, along with a couple of well-publicized case clusters. In at least one of these cluster episodes, multiple individuals who received allograft tissue implants were either severely sickened or died due to contaminated allografts. There may have been more allograft infections than we know about because of gaps in our reporting system.

MIC: How have sterilization technologies affected allograft surgery?

Dr. Sapega: Several proprietary methods of allograft tissue processing have been developed over the years that reduce or

The Clearant process kills all bacteria and destroys or inactivates all viruses, whether in soft tissue allograft implants or hard tissue (bone) allograft implants.

—Alexander A. Sapega, M.D., New Jersey Knee and Shoulder Center

effectively eliminate the chance of infectious disease transmission from a contaminated allograft tissue specimen. While it is my understanding that only the Clearant process is the practical equivalent of medical "sterilization," in my opinion, *any* method of tissue processing that reduces the chance of infectious disease transmission is better than none, as long as the tissue treatment process does not compromise the structural properties and integrity of the tissue implant.

An article published in the *Journal of Orthopaedic Research* demonstrated to my satisfaction that the Clearant process was biologically effective, yet did not compromise the strength of treated tendon tissue implants. There is not as much scientifically validated and published data available for the other tissue treatment methods currently employed by some tissue processing vendors and tissue banks. However, I believe that the net effect of the availability of these newly developed tissue processing methods has increased the safety of allograft implant surgery.

As I noted above, my patients' receptivity toward the idea of allograft surgery has dramatically increased since I gained the ability to inform my patients that I could provide them with a "sterilized" tissue implant, rather than one that was merely harvested from the tissue donor using "aseptic technique" and then tested and screened by the tissue bank. From my own perspective as a surgeon, if I can offer a patient a sterilized allograft implant that has the same mechanical properties and function as would their own tissue, thereby allowing the patient to avoid the extra surgical morbidity associated with autograft tissue harvesting, I believe the choice between autograft and allograft surgery becomes almost a "no brainer" in favor of allograft surgery.

MIC: How do sterilization technologies affect the integrity of the allografts?

***Dr. Sapega*:** As I noted above, this is an important question. One of the earliest methods of allograft tendon sterilization, which was employed for a while approximately 15 to 20 years ago, was high dose irradiation administered at room temperature. While this effectively sterilized the allograft implant, to some extent it also "cooked" it, thereby compromising its strength and other mechanical properties. This ended up impacting the clinical outcome of patients in a negative way, thus radiation-sterilized allograft implants quickly fell out of favor with surgeons. It was not until the newest generation of tissue processing techniques was developed that surgeons and patients once again began getting interested in allograft tissue treatment prior to implantation.

MIC: What clinical data is available that supports the use of sterilization?

***Dr. Sapega*:** So far, I am unaware of any cases of infectious disease transmission by way of a "sterilized" allograft tissue implant. All reported infections have occurred with untreated allografts. Additionally, the early clinical results of patients who have had their knee ligaments reconstructed with Clearant sterilized allografts have shown no compromise in the surgical success rate due to the use of the Clearant process. Patients who have a Clearant processed allograft implanted in their knee, as far as investigators have been able to determine thus far, can expect the same clinical outcome following surgery, yet effectively without any risk of infectious disease transmission.

MIC: What is the Clearant process?

***Dr. Sapega*:** The Clearant process is the first allograft tissue processing technology with a demonstrated capability of substantially reducing all types of pathogens in tissue implants, while maintaining the integrity of the tissue's essential underlying protein. The Clearant process kills all bacteria and destroys or inactivates all viruses, whether in soft tissue allograft implants or hard tissue (bone) allograft implants. The Clearant process is also capable of preventing problems associated with contamination by fungi, yeast and spores. The Clearant process utilizes a high enough dose of gamma radiation energy to sterilize tissue, but this energy is applied under defined, low-temperature conditions. Before this treatment the tissue implants are preconditioned by soaking them in a biocompatible radioprotective solution developed by Clearant. The patented Clearant process dramatically reduces the production and damaging effect of free radicals within the treated tissue, this being one of the means by which the older, more primitive methods of gamma sterilization damaged the mechanical integrity of the tissue implants.

MIC: What distinguishes the Clearant process from other available technologies?

Dr. Sapega: In my mind, several things. First, I find it quite comforting that the Clearant process has been *proven* effective in reducing the risk of potential allograft-related infection to a level that is so low that it meets the practical definition of "sterility," as defined by the FDA.

Second, the tissue penetrating capability of gamma radiation energy, particularly for larger allograft specimens and bone, is superior as compared with the alternative chemical wash or soak processing methods available.

Third, I very much appreciate the feature of the Clearant process that the allograft specimen is sterilized *within* its *final* packaging, precluding a cross-contamination mishap after the sterilization procedure during final preparation and packaging at the tissue bank. Even if a tissue sterilization procedure were 100 percent effective, if that tissue specimen must be handled afterward in order to finish processing it and package it, there is a chance for inadvertent contamination during this final phase. This is something that neither I or my patients need worry about with Clearant sterilized allografts.

MIC: Have other processes been proven to be effective in the past?

Dr. Sapega: The original, high-dose gamma irradiation method employed 15 or 20 years ago was proven efficacious in sterilizing allograft tissue implants; however, the drawback was compromised allograft mechanical properties and increased surgical failures. Even though the idea of sterilizing allograft tissue implants was certainly a good one, if the allograft sterilization process materially compromised the results of surgery, it was not worth employing. The risk of infectious disease transmission from an allograft specimen was statistically quite low to begin with, so those patients who chose allograft surgery simply decided that they would accept this very small risk and have their surgery performed using aseptically harvested and packaged tissue implants rather than sterilized implants.

As for the efficacy data available for the other newly developed tissue processing methods aside from the Clearant process, I have not yet come across published results about this, as I have for the Clearant process. It is my understanding there is a lot of ongoing research and testing being performed by the various entities who have developed competing tissue treatment processes. I look forward to seeing this published research when it becomes available. In particular, I am looking for a tissue treatment process that is FDA-approvable for meniscus allograft implants, for which the Clearant process has not yet been approved. Right now, I can only obtain Clearant processed tendon and bone implants for my patients, not cartilage transplants.

MIC: What is the difference between sterility and viral inactivation?

***Dr. Sapega*:** The FDA defines sterility in reference to microbial organisms only (bacteria, fungi, yeast and spores), and does not include viruses. For viruses, rather than use the term "sterilization," the FDA has defined "viral inactivation." The Clearant process utilizes the standard set by the FDA to determine the "inactivation" of viruses, including HIV, hepatitis C, hepatitis B and West Nile Virus, so the Clearant process obviates the risk posed by these most common viral worries to both patients and surgeons alike. I have read that the Clearant process is capable of inactivating both lipid-enveloped and nonenveloped viruses, DNA and RNA viruses, double- and single-stranded viruses, etc.

MIC: Are sterile implants costly?

***Dr. Sapega*:** When I first inquired with Clearant regarding the availability of treated tendon implants for my patients, I asked about the added cost. The initial cost to the patient or surgical facility may vary depending upon the tissue bank from which the implant is obtained, but I was informed that the addition of Clearant sterilization adds approximately $65 to the cost of the implant. That did not strike me as being unreasonable. I thought if I were a patient, and my insurance was not going to cover this additional sterilization cost, I would most certainly be willing to put that $65 out of my own pocket in order to obtain a guaranteed sterile implant. So far, none of my patients have had to pay anything extra, out of pocket, in order to obtain a Clearant processed allograft. However, I suppose this might occur at some point in the future, depending upon which insurance company might be involved in covering one of my patient's surgical procedures.

MIC: How have sterilization guidelines changed over the years?

***Dr. Sapega*:** Prior to 1993, there was no government oversight or regulation of the tissue transplant industry. In 2005, the FDA put into place a regulation that required bone and tissue banks to follow good tissue procurement and handling procedures (the "Current Good Tissue Practices" guideline). These recommended procedures do not require tissue "sterilization," and relate more to testing and handling of allograft tissue implants. At the present time, the FDA has convened a working group or task force to reconsider the regulation of allograft tissue procurement and processing methods employed by bone and tissue banks in the United States. The FDA may or may not come out with a strong recommendation or requirement for tissue "sterilization," over and above the usual good tissue processing and handling methods already recommended.

One thing I believe they definitely *should* be focusing on, for the general public's safety, is the initial, weakest link in the allograft tissue supply chain, this being *procurement*. Recently, a few well-publicized incidents of improper and/or fraudulent tissue procurement occurred, which caused a number of otherwise well regarded tissue banks and suppliers to be provided with inappropriately harvested and potentially contaminated tissue specimens. Tissue banks must generally rely upon the integrity of local tissue procurers, and I believe there are far more procurers than there are certified bone and tissue banks. That is why I believe that procurement is the weakest link in the tissue supply chain in our nation.

While an across-the-board use of tissue sterilization methods such as the Clearant process, in all bone and tissue banks today, would essentially obviate the risk posed by unethical/fraudulent local tissue procurers, I still believe that the allograft tissue supply chain in our nation should be thoroughly supervised and regulated by the FDA. First, not all types of tissues can withstand currently available sterilization procedures. Second, there currently exists a significant supply/demand imbalance with respect to allograft tissue implants, which I believe will worsen with the increasing popularity of allograft surgery among patients, given the development and availability of tissue sterilization methods such as the Clearant process.

Whenever a significant supply/demand imbalance exists, and there is money involved, the risk of unethical behavior by a small minority of individuals will always exist. I firmly believe that both tissue banks *and* surgeons have a role to play in protecting patients from this risk, even if the risk is statistically small. This was one of the reasons that I first became interested in the Clearant tissue allograft sterilization process, and once I learned more about it, I incorporated it into my clinical practice and began offering it to my patients. ✛