CryoLife Update: Allograft-Associated Bacterial Infections-United States, 2002

News reports following a Center for Disease Control and Prevention's (CDC) update regarding allograft-associated bacterial infections (MMWR March 15, 2002) have generated confusion regarding infections in orthopaedic surgeries involving soft tissue allografts. The CDC's update dealt with 26 reported infections and one death over the past four years in orthopaedic surgeries that involved soft tissue allografts obtained from 4 or 5 tissue processors. The update identified that 14 of the reported infections during the four-year period involved orthopaedic surgeries in which CryoLife processed tissues were implanted.

The confusion from news reports following this update reached its peak with a Reuters report issued the afternoon of March 15, 2002. That report, picked up by other sources and reported as fact, apparently misconstrued earlier reports and stated that 14 patients had died from infected allograft tissues. No such event was reported in the CDC update. Reacting to the confusion, several hospitals, surgeons and patients have inquired of us about allograft safety, our processes, our rates of infection and our reaction to the CDC report.

Some relevant facts are:

1. SINCE 1997, THE REPORTED INCIDENCE OF INFECTION IN ORTHOPAEDIC SURGERIES INVOLVING THE USE OF SOFT TISSUE ALLOGRAFT IMPLANTS PROCESSED BY CRYOLIFE IS APPROXIMATELY 0.2%.

2. THE REPORTED INCIDENCE RATE OF INFECTION IN GENERAL U.S. ORTHOPAEDIC SURGERIES IS BETWEEN 0.6% AND 2.2%.[1]

3. NOT ALL OF THE REPORTED 26 INFECTIONS IN THE UPDATE HAVE BEEN DEMONSTRATED TO BE LINKED TO THE USE OF IMPLANTED SOFT TISSUE ALLOGRAFTS. OTHER SOURCES CAN, AND DO, CAUSE INFECTION IN SURGERIES.

4. MOST OF THE RECOMMENDATIONS MADE BY THE CDC IN ITS REPORT FOR THE TISSUE PROCESSING INDUSTRY ARE ALREADY INCORPORATED INTO CRYOLIFE'S PROCESSING PROCEDURES. OTHER RECOMMENDATIONS ARE BEING SERIOUSLY REVIEWED.

5. CRYOLIFE IS COMMITTED TO PATIENT SAFETY. TISSUE PROCESSING IS CONDUCTED IN STATE-OF-THE-ART FACILITIES USING TESTING AND PROCESSING METHODS DESIGNED TO REDUCE THE RISK OF INFECTION AND PROVIDE LIFE ENHANCING TISSUE IMPLANTS.

[1] Aggregated Data from the National Nosocomial Infections Surveillance (NNIS) System, December 2000, Centers for Disease Control and Prevention.

For more than 50 years, patients have greatly benefited from the implantation of soft tissue allografts, despite the absence of technologies that can assure sterility of soft tissue allografts without compromising their clinical performance. Finding ways to decontaminate and sterilize soft tissue allografts without compromising tissue performance are areas of active investigation throughout the industry, with CryoLife in the forefront of this research.

There is no accreditation process or regulatory oversight by any organization, public or private, mandated or voluntary, that, by itself, guarantees the safety of allograft tissue. Indeed, this level of assurance rarely exists with any medical technology, product or service used in sophisticated surgical procedures.

CryoLife has been a leader in the tissue preservation industry for over 18 years, and during this time we have provided over 150,000 soft tissue allografts for implant. CryoLife has worked hard through the years to earn and maintain a superior level of confidence in the integrity of our processing procedures. We have always based our operating procedures on science. Our primary objective is to provide allografts of the highest safety and quality for surgeons and their patients.

To that end, we want to review the methods we use to process safe allograft tissues. And in doing so, we will discuss the following topics:

- Microbial Testing
- Refrigeration
- Infection Rates and Allograft Tissues
- CDC Recommendations

Microbial Testing

Recent reports have created significant confusion regarding microbial testing and its ability to guarantee tissue safety. Sampling is the current method for detection of microbial contamination. CryoLife has always tested for the presence of both aerobic and anaerobic microbial contamination and discards all tissue with positive cultures. Common methodologies for microbial testing in the industry include destructive testing and swabbing of companion samples. However, neither of these methods can be 100% effective in the detection of all microbial contamination.

Destructive Testing

CryoLife performs destructive testing of companion samples of donated human tissue as its method of microbial detection. These companion tissue samples originate from either portions of the tissue not used for transplant or from sites that are adjacent to the implantable tissue. Destructive testing is capable of detecting contamination on the surface and within the entire sample. While complete destructive testing of the entire graft is the most effective methodology

it, of course, can only be employed with companion samples rather than the implantable allograft itself. Destructive testing of the entire allograft was needed by the CDC to detect *Clostridium sordelli* in the case mentioned in their report. Since sampling must be used in microbial testing, the limits of sampling must be acknowledged. For example, the CDC was able to test 19 allografts from the donor associated with the *Clostridium sordelli* infection in Minnesota, of which 17 of the allografts (89.5%) were free of microbial contamination. This clearly demonstrates the potential limitations of microbial sampling to assure absolute safety in the use of allografts. Indeed, as the CDC test results show, the presence of *Clostridium sordelli* might not have been detected even if destructive testing of more than half of these allografts from this specific donor had occurred. The sampling methods employed throughout the tissue processing industry have these same limitations.

Swabbing

CryoLife does not currently use the method of swabbing tissue because we have found that swab culturing 1) is effective only in the detection of gross surface contamination, 2) may introduce microorganisms in the process, 3) may produce false positives which will limit the use of donated tissue and 4) does not guarantee that the entire graft is free of microbial contamination. The only testing method capable of detecting all microbial contamination involves the total destruction of the implantable allograft.

Refrigeration

The MMWR report dated March 15, 2002, by the CDC, inferred that extended procurement time was potentially a major contributing factor in the incidence of clostridial infections; however, it should be noted that the current published limits for refrigeration and recovery time are based largely upon arbitrarily selected traditional practices. Procurement of tissue within AATB guidelines for refrigeration and recovery does not guarantee freedom from infection (as many as 25 of the reported infections in the MMWR report were associated with tissue procured within the AATB recommendations for both refrigeration and recovery time). The entire industry needs more scientific data in order to maximize the balance between soft tissue allograft availability and safety. Efforts should be made to base decisions on scientific data rather than arbitrary guidelines.

Infection Rates and Allograft Tissues

Overall infection rates for orthopaedic surgeries are reported to be between 0.63% and 2.20%. In comparison, the reported rate of infection in surgeries involving CryoLife processed orthopedic allografts over the past five years is approximately 0.2%. Our data represent all reported infections, whether confirmed or not, associated with surgery involving a CryoLife-processed orthopaedic graft. Moreover, even when a patient experiences an infection post surgery, identification of the allograft as the source of the infection is problematic because in many cases it is extremely difficult to isolate the cause of infection. Environmental conditions, surgical instrument sterility and breach of sterile technique can all contribute to infection in any orthopaedic surgical procedures. CryoLife follows all procedures for medical device complaint handling and MedWatch reporting. This assures that CryoLife's data regarding reporting

infection rates are accurate and complete. Furthermore, we believe the entire industry should operate to these standards.

CDC Recommendations

In the MMWR, report the CDC made a number of recommendations for the entire tissue banking industry. Among the CDC recommendations are five practices that CryoLife has ALWAYS followed:

1. *After receiving 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 the infection.*
   CryoLife procedure not only follows this recommendation, but also goes further by recovering any allografts from that donor that have been shipped but not implanted.

2. *Tissue processors should contact healthcare providers of recipients of tissue from the same donor implicated in an allograft-associated infection.*
   CryoLife follows this practice.

3. *Samples of such nonimplanted tissues from the same donor that are recovered and that underwent the same processing method as the potential allograft-associated infection should be cultured by an independent laboratory using a validated method.*
   CryoLife has a complaint investigation system and does utilize appropriate independent services when necessary.

4. *Unless a sporacidal method is used, aseptically processed tissue should not be considered sterile, and healthcare providers should be informed of the possible risk for bacterial infection.*
   CryoLife's packaging insert contains a warning box stating, "...there is no assurance that the tissue is free from infectious diseases or microbial contamination." Furthermore, under the precautions section CryoLife states, "due to the nature of this tissue, a post-operative prophylactic regimen of antimicrobials should be considered."

5. *Culture methods should be validated to ensure that residual antimicrobials do not result in false-negative culture results.*
   CryoLife employs fully validated, state-of-the-art, automated aerobic and anaerobic microbial detection methods. Any positive culture results in the destruction of the tissue associated with that sample. The CDC also made a specific recommendation to enhance the performance of this system, which CryoLife has implemented.

The CDC also made recommendations that are currently not feasible but which deserve attention by the industry.

1. *When possible, a method that can kill bacterial spores should be used to process tissue.*
   We agree with the CDC, that the employment of a method to kill bacterial spores would decrease the possibility of infection. As documented by the CDC, irradiating soft tissue

using current techniques does not guarantee the sterility of the tissue. There is no known technology which is sporicidal and which maintains the integrity of soft tissue. Three patients mentioned in the CDC report received allografts that were reported to have undergone gamma irradiation. CryoLife is dedicating significant resources to develop new techniques and technologies that will kill spores while maintaining tissue integrity.

The CDC also had the following recommendations:

1. *Tissues should be cultured before suspension in antimicrobial solutions and if Clostridium or other bowel flora are isolated, all tissue from that donor that cannot be sterilized should be discarded.*
   CryoLife formerly cultured samples of *all* tissue before suspension in an antimicrobial solution but discontinued this practice after determining that it did not increase the safety of the tissue. Nevertheless, CryoLife is evaluating pre-culturing specific tissues to determine if this process actually results in increased safety.

2. *Perform both destructive and swab cultures on all tissues.*
   Please refer to microbial testing section.

3. *Recommended time limits on tissue retrieval should be followed.*
   Please refer to refrigeration section.

4. *Perform an audit of CryoLife's entire unreleased tissue inventory to estimate the proportion of tissue that may be contaminated with microorganisms or spores.*
   CryoLife acknowledges that there may be academic value to such an audit, but has elected not to initiate such a study at this time for several reasons. First, such an audit would not add to the basic understanding that some allografts are likely to demonstrate the presence of microorganisms. Second, since current methods of processing tissue are frequently at the limit of known technology, such an audit cannot effect an improvement unless there is an industry-wide adoption of sterilization despite its adverse effects. Third, such an audit, to be statistically valid, would require the destruction of a large number of vitally needed, irreplaceable implants. Finally, for such an audit to be truly useful to the industry, such an audit must involve industry-wide participation so that universal processing and testing techniques now employed by the industry and their relationship to the microbiological status of final processed tissue can be evaluated.

Conclusions

1. Since the inception of tissue banking in 1947, hundreds of thousands of patients have experienced a significant improvement in their quality of life, thanks to the donation, processing and distribution of soft tissue allografts.

2. CryoLife is the leader in the cryopreservation of soft tissue allografts. Since its inception, it has advanced the science of cryopreservation and has introduced many new tissues that have gone on to benefit thousands of patients.

3. CryoLife is committed to improving the safety of the tissue it processes. We believe that until a validated sterilization process is developed that will not compromise tissue integrity, the risk of infection, albeit demonstrably small, cannot be eliminated. The surgical community and tissue processing industry must acknowledge the limitations of sampling as a primary method of microbial detection.

4. Until sterilization technology advances to the point of being able to guarantee sterility of soft tissue allografts, CryoLife will continue to recommend in its labeling that a postoperative prophylactic regimen of antimicrobials should be considered. This is consistent with the CDC's recommendation.

5. The risk of infection associated with soft tissue allografts is very low. CryoLife's reported infection rate is approximately 0.2%, compared to overall infection rates between 0.6% and 2.2% for orthopaedic surgery.

6. While we are in agreement that there are improvements that can and should be made throughout the tissue processing industry, we are concerned that the media's treatment of the CDC report may have caused unnecessary confusion and concern in the medical community.

7. Refrigeration and warm ischemic time limits need to be studied by the industry. Efforts should be made to base decisions on scientific data rather than arbitrary guidelines.

8. Based on the CDC report, CryoLife has made some changes to its processes and is dedicating significant resources to develop new techniques and technologies that will improve tissue safety while maintaining soft tissue integrity without compromising clinical performance.

James C. Vander Wyk

James C. Vander Wyk, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance

CryoLife®, Inc.
Biotechnologies for Medicine™

1655 Roberts Boulevard, NW • Kennesaw, Georgia 30144
Phone: 770-419-3355 • 800-438-8285 – US & Canada
Fax (770) 590-3742 Website: www.cryolife.com

ML0108.000