MUSCULOSKELETAL ALLOGRAFT TISSUE SAFETY

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TISSUE WORK GROUP

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BASIC AWARENESS

The use of musculoskeletal allograft tissue in reconstructive orthopaedic procedures has markedly increased over the last decade. (Figure 1)

Surgeon knowledge of tissue bank practices in donor consent and screening, serology testing and processing is important when making the decision to use these allograft tissues.

The orthopaedic surgeon also has the responsibility to inform the patient about the risks, benefits and alternatives of using allograft tissue.

This handout provides an overview of some of these issues.

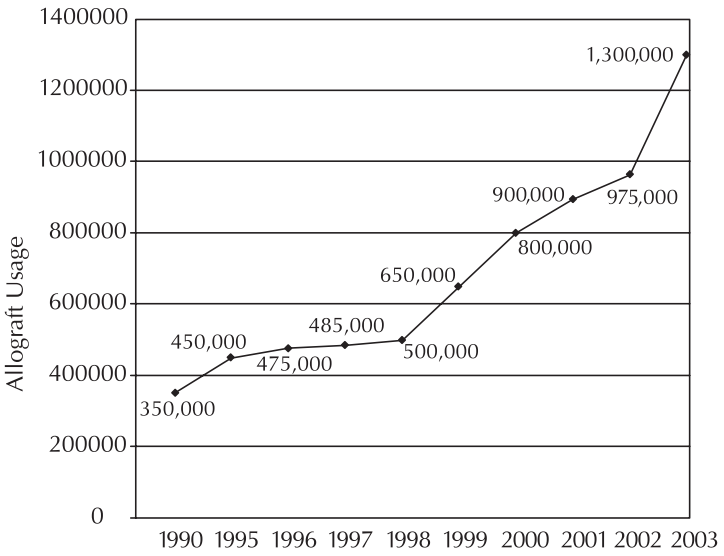

Figure 1: Musculoskeletal allograft distribution. Source: AATB Annual Survey. (2004, 2005 numbers not available)

What are the Commonly Used Allografts in Orthopaedic Procedures?

Bone

- Demineralized bone products (osteoinductive)
- Cortical/cancellous – powder, chips, wedges, dowels, crest, pegs and screws
- Structural – cortical segments, shafts, long bones, pelvis, acetabulum
- Osteochondral long bone (cryoprotected cartilage)
- Ribs, mandible, calvarium, ear ossicles

Soft Tissue

- Patellar ligament and Achilles tendon (bone block), other assorted tendons
- Fascia lata, rotator cuff

Cartilage

- Meniscus, osteoarticular segments (fresh and cryoprotected), costal cartilage

Figure 2: Bone-patellar tendon-bone allograft.

Figure 3: Processed iliac crest wedge.

Figure 4: Femoral allograft.

What are the Milestones in Tissue Banking?

1881	First human bone transplant under aseptic conditions
1925	Lexer: First reported large series of bone transplants (50% success rate)
1950	U.S. Navy Tissue Bank established in Bethesda, Maryland (George Hyatt, M.D.)
1955	Low temperature preservation of bone (reduction of antigenicity)
1960s	Early reports of successful use of tissue implants
1972	Ottolenghi: Long bone/osteoarticular allografts series
1973	Parrish: Long bone allograft replacement series
1983	Mankin: Two hundred large bone allograft series
1984	First *Standards for Tissue Banking* published by the American Association of Tissue Banks (AATB)
1986	AATB Inspection/Accreditation Program initiated
1989	AATB Training and Certification Program for Tissue Bank Specialists (CTBS)
1993	FDA: Interim Rule, Human Tissue for Transplantation (FDA inspection of tissue banks initiated)
1994	AATB Inspection/Accreditation Program using contract, non-affiliated inspectors
	CDC: Guidelines for Preventing HIV Transmission Through Transplantation of Human Tissue and Organs
1997	FDA: Final Rule, Human Tissue for Transplantation
2001	FDA: Final Rule, Establishment Registration and Product Listing FDA: Proposed Rule, Good Tissue Practices; Inspection and Enforcement
2002	FDA: Guidance Document - Validation of Procedures for Processing of Human Tissues Intended for Transplantation
2003	More than 1,300,000 musculoskeletal allografts distributed in the U.S.
2006	98 AATB Accredited Tissue Banks (Consult AATB Web Site at www.aatb.org)

Figure 5: First depicted allograft transplantation. 12th Century painting of Saints Cosmas and Damian. (circa 3rd century)

Figure 6: AATB Standards.

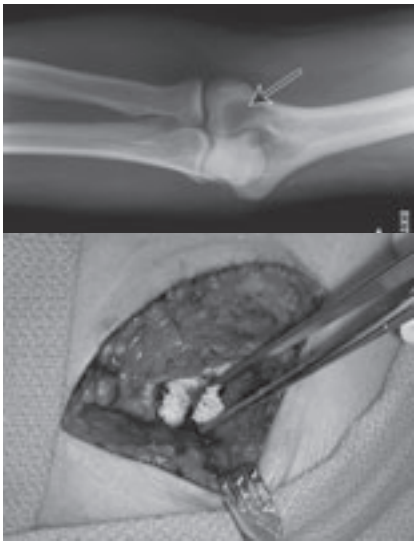

Figure 7: 16-year-old with aneurysmal bone cyst; repair using bone graft cancellous chips.

What has Occurred in Government Regulation?

1968	Uniform Anatomical Gift Act (UAGA) provided to states for adoption and enactment
1984	National Organ Transplant Act
1985	HIV antibody testing (FDA) for blood donors
1990	HCV antibody testing (FDA) for blood donors
1993	FDA: Interim Rule, Human Tissue Intended for Transplantation
1995	JCAHO oversight in tissue banking (limited to Laboratory inspection manual)
1997	FDA: Final Rule, Human Tissue Intended for Transplantation, and Guidance Document, Screening and Testing of Donors of Human Tissue Intended for Transplantation
1997	FDA: Proposed Approach to Regulation of Tissue Products (Tissue Action Plan)
1998	Medicare Requirements for hospital participation in organ/tissue donation
1999	FDA: Proposed Rule: Suitability Determination for Donation
2000	FDA: Blood Donor Testing of HIV RNA and HCV RNA by PCR (NAT) FDA: Guidance Document, Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens
2001	FDA: Proposed Rule for Good Tissue Practices FDA: Final Rule: Establishment Registration and Listing, Manufacturers of Human Tissue Products OIG (Office of the Inspector General): reports on Informed Consent and, Oversight of Tissue Banking
2002	FDA: Guidance Document, Validation of Procedures for Processing of Human Tissue Intended for Transplantation FDA: Draft Guidance Document, Preventive Measures to Reduce the Possible Risk of Transmission of CJD and vCJD by Human Tissue (HCT/Ps)
2004	FDA: Final Rule and draft Guidance Document - Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/P) (the Rule was effective May 25, 2005) FDA: Final Rule, Current Good Tissue Practice (CGTPs) for HCT/P Establishments; Inspection and Enforcement (Effective May 25, 2005)
2005	JCAHO: Tissue Storage and Issuance Standards for hospitals and surgical centers FDA: Guidance Document, MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

What Practical Steps are Taken in Tissue Banking in Assessment and Processing?

Detailed inquiry into donor's medical, social and sexual history (including autopsy if performed)

Donor Screening: Medical History and Behavioral Risk Assessment

At Time of Donation, Exclusionary Criteria:

- Active infection, sepsis, or TB
- History of systemic viral illness (Hepatitis, HIV, recent West Nile Virus, etc.)
- Untreated syphilis, Hansen's Disease
- Certain autoimmune diseases
- Ingestion of toxic substances that may affect tissues
- Rheumatoid arthritis, systemic lupus, polyarteritis nodosa, and sarcoidosis
- Clinically significant metabolic bone disease
- Clinically significant malignancy
- Implantation of dura mater or use of human derived pituitary growth hormone (Spongiform Disease, CJD)
- Risk factors associated with HIV, Hepatitis, sepsis, HTLV infection, WNV, SARS, malaria
- Dementia of infectious or unknown etiology

Donor Screening: Physical Assessment

Examination of Potential Donors Includes Looking for Evidence of:

- Active infection: viral, bacterial or fungal
- Sexually transmitted diseases such as genital ulcerative disease: herpes simplex, syphilis and chancroid
- Needle tracks (nonmedical); recent tattoos and piercings (within past 12 months)
- Lymph node enlargement
- Jaundice, icterus, hepatomegaly
- Blue/purple (gray/black) spots consistent with Kaposi's sarcoma
- Evidence of anal intercourse (perianal condyloma, insertion trauma)
- Oral thrush
- Trauma to recovery sites
- Clinically significant skin lesions (rash, scabs)

Infectious Disease Testing

Tests Required by FDA; performed by CLIA-registered or CMS-approved laboratories:

- HIV 1/HIV 2 Antibody
- HB Core Antibody (total, IgM + IgG)
- HB_sAg
- HCV Antibody
- Syphilis (T. pallidum)

  Reference: FDA CGTP Rule and draft Donor Eligibility Guidance Document

AATB Required Additional Testing:

- HTLV-I/II Antibody
- HIV-1 NAT
- HCV NAT

Window Period
Period between infection and time virus is detectable by screening tests.

	Virus	
	HIV	**HCV**
Window Period using FDA Licensed Tests	HIV antibody 22 days NAT* - 7 days	HCV Antibody 70 days NAT* - 7 days
Blood Donor Estimated Risk (repeat donor)(a)	with NAT* 1:2 million	with NAT* 1:2 million
Tissue Donor Estimated Risk (b)**	without NAT* 1:55,000 with NAT* 1:173,000	without NAT* 1:42,000 with NAT* 1:421,000

*Nucleic Acid-Amplification Test
Source: (a) Stramer et al, NEJM 351:760-768, 2004
(b) Zou et al, NEJM 351:751-759, 2004
*** This is difficult to estimate for tissue donors because of increased prevalence and smaller donor pool. Tissue processing methods validated to kill viruses are not included in this risk estimate.*

Tissue Processing

- Audited or accredited facility following current Good Tissue Practices
- Possesses a Quality Control/Quality Assurance Program
- Elimination or reduction of blood, debris and cells from allografts to reduce disease transmission potential
- Validation of bacteriologic and virucidal washes and/or treatments
- Evaluation of bacteriologic bioburden (pre-processing and in-processing cultures to evaluate contamination)
- Possible use of gamma radiation 1.5 Mrads (15 kilogray) or more (pre-processing or terminal sterilization)
- Final product testing for bacteriologic contamination (swabs, immersion, or destructive testing)
- Potential discard of tissue or donor lot based on certain types of early bacteriologic contamination (*Streptococcus Group A, Clostridium*)
- Final review by tissue bank medical director of screening/testing prior to release of tissue for transplantation

Sterilization (Selected Tissues) for Microorganisms

- Gamma or E beam radiation 1.5 - 2.0 Mrads [15 - 20 kilogray] (these amounts or higher may raise concern for integrity of tissues especially soft tissues)

DONATE LIFE America

What are the Episodes of Documented Disease Transmission?

Over the past decade more than 6 million musculoskeletal allografts have been safely transplanted in the United States. Relatively few incidents of disease transmission have been reported:

Mycobacterial: Tuberculosis
- One case (four recipients): *James et al, JBJS 35B:578, 1953*

Bacterial:
- One case: *Tomford et al, JBJS 63A:244-248, 1981*
- Three cases: *Lord et al, JBJS 70A:369-376, 1988*
- Cases investigated by CDC: *MMWR 50(48):1080-1083, December 7, 2001 and MMWR 51(10):207-210, March 15, 2002*
  Situation One:
  - ♣ Death November 2001 Clostridium sordellii
    Fresh osteochondral femoral allograft segment in 23 y/o male

  Situation Two: Tissue from same donor - tissues were irradiated
  - ♣ Patient A bone-tendon-bone; Pseudomonas aeruginosa, Staph. aureus, Enterococcus
  - ♣ Patient B bone-tendon-bone; Pseudomonas aeruginosa

  Situation Three: Tissue from same donor - radiation planned but not accomplished
  - ♣ Patient A bone-tendon-bone; Citrobacter werkmanii youngae; Group B Streptococci
  - ♣ Patient B bone-tendon-bone; Klebsiella oxytoca/Halfnia alvei
- One case: bone-tendon-bone; Group A streptococcus: *MMWR 52(48):1173, December 5, 2003*
- 14 probable Clostridium cases: *Kainer et al, NEJM 350:2564-2571, 2004* Major findings include:
  - ♣ Clostridium infections traced to allograft implantation (occurring between Jan 1988 to Mar 2002); all "sports medicine" allografts; all processed by one tissue bank not accredited by AATB
  - ♣ Gaps identified include lack of pre-processing cultures and probability of false negative cultures due to culturing method used post-processing
- One case: soft tissue for ACL, Chryseobacterium meningosepticum, Rx antibiotics, graft not removed: *AP article, September, 2006*

Viral: Hepatitis B - One case: *Shutkin, JBJS 36A:160-162, 1954*
Hepatitis C - One case: *Eggen and Nordbo, NEJM 326:411, 1992*
Two cases: *Conrad et al, JBJS 77A:214-224, 1995*
Four cases: three bone-tendon-bone (non-irradiated) and one tendon: *MMWR 52(13):273-276, April 4, 2003; Tugwell et al, Transmission of Hepatitis C Virus to Several Organ and Tissue Recipients from an Antibody-Negative Donor, Annals of Internal Medicine 143(9):648-654, 2005*

HIV - One case: *MMWR 37(39):597-599, 1988* (pre-HIV antibody testing)
Three cases: *Simonds et al, NEJM 326:726-732, 1992* (tissue retrieved 1985)

What is the Message?

- Estimated that 1.5 million musculoskeletal allografts distributed in US in 2006.
- Disease transmission is rare when comparing reports of infection vs number of allografts distributed/yr.
- Tissue availability is predicated on the gracious altruistic act of numerous donors and donor families.
- Conventional sterilization techniques used for metallic implants may adversely affect functional, biological and mechanical properties of soft tissue allografts.
- No reports of disease transmission using demineralized bone products.
- Some grafts can be treated with 1.5 Mrads (15 kilogray) or more to reduce/eliminate contamination. This may affect properties of the allograft.
- Inherent safety of the graft is based upon Current Good Tissue Practices and AATB Standards:
  - Donor screening and physical assessment
  - Infectious disease testing
  - Validated processing techniques
  - Attention to quality control/quality assurance
- Suspected allograft-caused infections must be reported to the tissue source facility (JCAHO Standards); can voluntarily be reported to FDA (www.fda.gov/medwatch/); or are reported to FDA if participating in the MedSun project.
- No transmission of disease has been confirmed to date involving BTS recall (approximately 15,800 grafts implanted)
- Need outcome studies to improve safety and efficacy.
- Orthopaedic surgeon needs to know "the tissue banker".
- Surgeon/patient interaction regarding the risks and benefit of using allograft tissue in their procedure is requisite.