MUSCULOSKELETAL ALLOGRAFT TISSUE SAFETY

IMPROVING SAFETY BY KNOWING THAT YOUR ALLOGRAFT HAS NOT BEEN RECALLED OR QUARANTINED

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AWARENESS

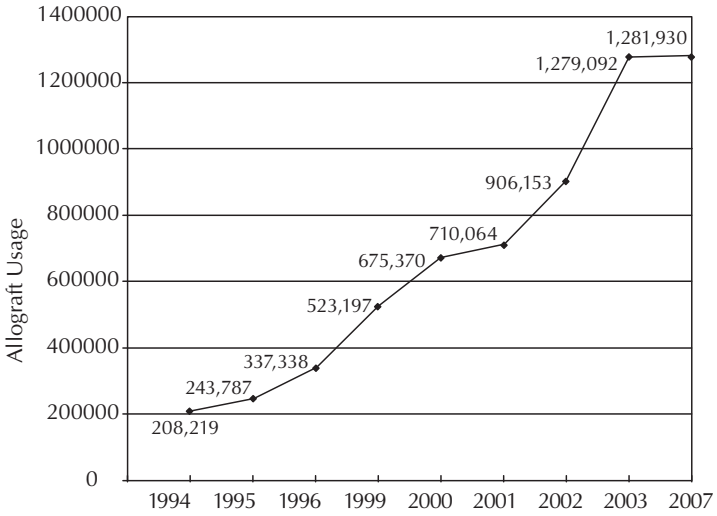
The use of musculoskeletal allograft tissue in reconstructive orthopaedic procedures has markedly increased over the last decade.

Surgeon knowledge of tissue bank practices in donor consent and screening, infectious disease 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.

Tissue recalls have occurred but hospitals were unable to identify all recipients or determine final disposition of the recalled tissue.

This exhibit provides viewpoints that support a paradigm change. Imagine a national, real-time web-based system that contains a database for donor and allograft registries with systems built in that enhances widespread communication when an adverse event/reaction occurs. If participation by stakeholders is high, immediate identity of tissue that has been recalled could be realized at the hospital and an allograft not inadvertently used before official notification of recall is sent. Compliance by end users to such a web-based system would eliminate the need for completion and mailing of tissue usage cards (see The Joint Commission, Transplant Safety Chapter at Standard TS.03.02.01, EP 7.)



Bone allograft distribution.
Source: AATB Annual Survey.

FDA RECALLS: HISTORICAL

From January 1994 through June 2007 there were 61,607 tissues recalled of which 96.5% were musculoskeletal tissues.

Last two major recalls:

- 2006 – BIOMEDICAL TISSUE SERVICES (NJ) ~ 28,000
- 2007 – CHRYSEOBACTERIUM RECALL (Musculoskeletal Soft Tissue) ~ 4,800
- There have been problems in identifying whether tissue has been used, stored or discarded at the hospital level.
- There has been recognized inadvertent use of recalled tissue after a recall was initiated.
- Some recalls (HIV Donor 1985) (HCV Portland donor 2000-2002) have occurred only after delayed recognition of transmission of infection to an organ transplant recipient from an organ and tissue donor, resulting in subsequent transmission to multiple tissue recipients.

Mroz, Joyce et al, J Am Acad Orthop Surg 16(10):559-565, 2008.

WHAT ARE THE EPISODES OF DOCUMENTED DISEASE TRANSMISSION?

Over the past two decades more than 10 million musculoskeletal allografts have been safely transplanted in the United States, but clinical consequences can be severe. Additionally, infectious disease risk is in part dependent on the degree of tissue processing. 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
- Two cases: soft tissue for ACL, Chryseobacterium meningosepticum, Rx antibiotics, grafts not removed: *AP article/Recall information, September, 2006*

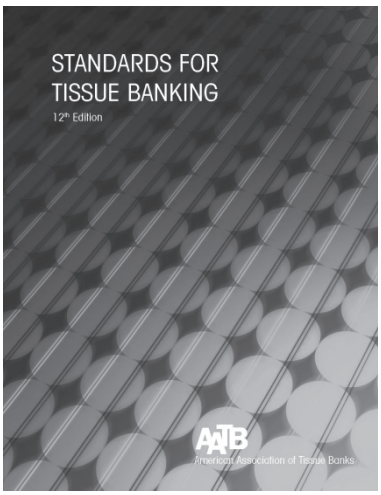
Viral:

Hepatitis B - One case: *Shutkin, JBJS 36A:160-162, 1954*

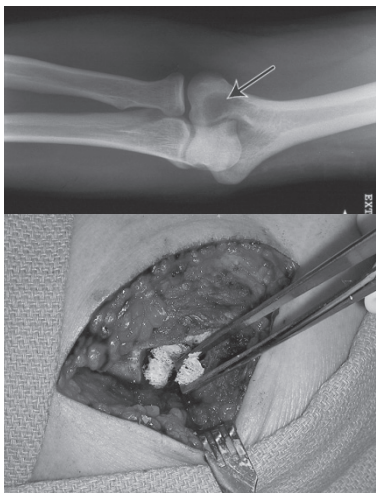
Hepatitis C - One case: *Eggen and Nordbo, NEJM 326:411, 1992*
Two cases: *Conrad et al, JBJS 77A:214-224, 1995*
Four cases: three bone-tendon-bone (non-irradiated) and one tendon: *MMWR 52(13):273-276, April 4, 2003; Tugwell et al, Ann Intern Med 143(9):648-654, 2005*

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

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



AATB Standards.



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

TRANSPLANTATION TRANSMISSION SENTINEL NETWORK (TTSN)

- 2005 CDC/FDA/HRSA organ and tissue safety workshop
    1. Unique donor ID linking organs and tissues
    2. Notification algorithm for trace-back and trace-forward tracking
    3. Clear mechanisms for adverse event reporting by healthcare facilities
    4. Better communications network within and between organ and tissue community
    5. Stronger information dissemination to broad array of clinicians, health professionals and patients
- Federal Grant to United Network for Organ Sharing (UNOS) with CDC to create TTSN to improve safety to all allograft recipients and establish a communication network.
- 3 Year Project
- Prototype TTSN system created with pilot project 2008: 1800 donations / 800 implants demonstrating functionality but areas of necessary correction needed to make the system work.
- Web-based electronic linkage of tissues and organs to this universal donor number by implanting facilities, allowing for rapid reporting of adverse events (reactions) in a secure national recipient database to be available to organ procurement organizations, eye and tissue banks.
- Online review for tissue recalls at the user institution/facility before a recipient procedure through pre-surgical checks with real time, web-based confirmation that there is no linked tissue recall or quarantine.
- System would eliminate need for mail completion and return of graft implant cards to the source tissue bank. The Joint Commission requirement would be met electronically instead.

Fishman et al, Cell Tissue Bank 10:271-280, 2009

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
- Exposure to toxic substances that may affect tissues
- Rheumatoid arthritis, systemic lupus, polyarteritis nodosa or 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 (including Group O), viral hepatitis, sepsis, WNV, malaria and vCJD
- 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 lesions, insertion trauma)
- Unexplained oral thrush
- Trauma or infection to recovery sites
- Clinically significant skin lesions (rash, scabs)

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.*

Infectious Disease Testing

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

- HIV 1/HIV 2 Antibody/HIV-1 NAT
- HB Core Antibody (total, IgM and IgG)
- HBsAg
- HCV Antibody/HCV NAT
- Syphilis test (T. pallidum)

Reference: FDA CGTP Rule and Donor Eligibility Final Guidance Document

Expectations of Tissue Processing

- Audited or accredited facility following current Good Tissue Practice
- Possesses a Quality Control/Quality Assurance Program
- Elimination or reduction of blood, debris and cells from allografts to reduce disease transmission potential
- Validation of washes and/or treatments that reduce or eliminate contamination
- Evaluation of bacteriologic bioburden (pre-processing and in-processing cultures to evaluate contamination)
- Possible use of gamma radiation 10-18 kilogray (10 kilogray ~ 1 Mrad)
- 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 10-18 kilogray (10 kilogray ~ 1 Mrad) (these amounts or higher may possibly raise concern for integrity of tissues especially soft tissues)

WHAT ARE THE MILESTONES IN TISSUE BANKING?

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 Practice; Inspection and Enforcement
2002	FDA: Guidance Document - Validation of Procedures for Processing of Human Tissues Intended for Transplantation
2009	More than 1,100,000 musculoskeletal allografts distributed by U.S. tissue banks
2009	106 AATB Accredited Tissue Banks (Consult AATB Web Site at www.aatb.org)
2009	Current Good Tissue Practice Regulation
2009	Draft Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues and Cellular and Tissue Based Products (HCT/Ps)

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	The Joint Commission oversight of tissue handling (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 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 Practice FDA: Final Rule: Establishment Registration and Listing, Manufacturers of Human Tissue Products OIG (Office of the Inspector General): 2 reports: Informed Consent; 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	The Joint Commission: Tissue Storage & 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)
2007	FDA: Final Guidance Document - Eligibility Determination for Donors of HCT/Ps (Effective August 28, 2007)
2008	The Joint Commission: Transplant Safety Chapter (appears in five accreditation manuals)

PUBLICATIONS FOR TISSUE MANAGEMENT IN THE HOSPITAL/ SURGICAL CENTER

- Section III. Transplanting Tissues in the new Transplant Safety Chapter of The Joint Commission's *Comprehensive Accreditation Manual* for each of the following: Hospitals, Critical Access Hospitals, Ambulatory Care, Office-based Surgery and Laboratory
- AABB (Previously known as American Association of Blood Banks) *Guidelines for Managing Tissue Allografts In Hospitals*
- AABB *Hospital Tissue Management: A Practitioner's Handbook*
- AATB *Standards for Tissue Banking*, Section L Tissue Dispensing Services (described management of tissues in a health care facility)

WHAT IS THE MESSAGE?

General

- ~ 1.5 million musculoskeletal allografts distributed in U.S. in 2007.
- Inherent safety of the graft is based upon following Current Good Tissue Practice and AATB Standards:
  - Donor screening and physical assessment
  - Validated processing techniques
  - Infectious disease testing
  - Attention to quality control/assurance
- Surgeon/patient interaction regarding the risks and benefit of using allograft tissue in their procedure is requisite.

Disease Transmission

- Disease transmission is rare.
- No reports of disease transmission using demineralized bone products.
- Risk of infectious disease transmission is greater for minimally processed musculoskeletal tissues.

Tissue Sterilization

- Conventional sterilization techniques used for metallic implants can adversely affect functional, biological and mechanical properties of soft tissue allografts.
- Some grafts can be treated with 10-18 kilogray (10 kilogray ~ 1 Mrad) or more to reduce/eliminate contamination. This may affect properties of the allograft depending upon the dosage.
- No transmission of disease has been confirmed to date involving BTS recall (approximately 15,800 grafts implanted).

Infectious Disease Reporting

- Orthopaedic surgeon needs to know "the tissue banker".
- Suspected allograft-caused infections:
  - Must be reported to the tissue source facility (Joint Commission Standards);
  - Can voluntarily be reported to FDA (www.fda.gov/medwatch/); or
  - Are reported to FDA if participating in the MedSun project

Challenges

- Tissue availability is predicated on the gracious altruistic act of numerous donors and donor families.
- Outcome studies are needed to establish safety and efficacy.
- A web-based system such as a Transplantation Transmission Sentinel Network would improve allograft safety through improved communication and data collection.

DONATE LIFE America