MUSCULOSKELETAL ALLOGRAFT TISSUE SAFETY

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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 gifting 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 and benefits of using allograft tissue.

This handout provides an overview of some of these issues.

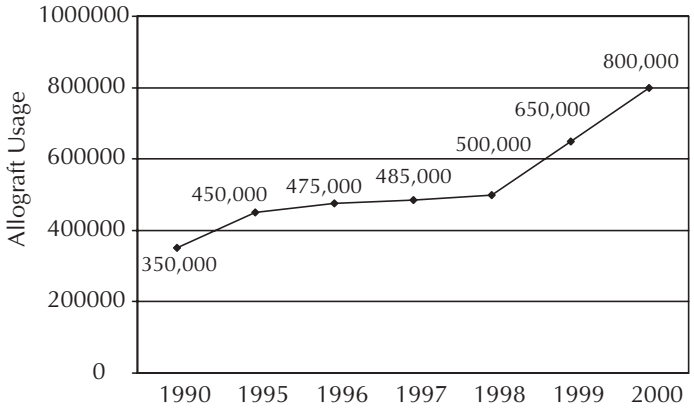


Figure 1: Musculoskeletal allograft usage. Source: U.S. Census Bureau, Statistical Abstracts of US 2001.

What are Commonly Used Allografts in Orthopaedic Procedures?

Bone

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

Soft Tissue

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

Cartilage

- Menisci, osteoarticular segments, costal cartilage

Figure 2: Bone-patellar tendon-bone allograft.

Figure 3: Dowel and iliac crest allograft.

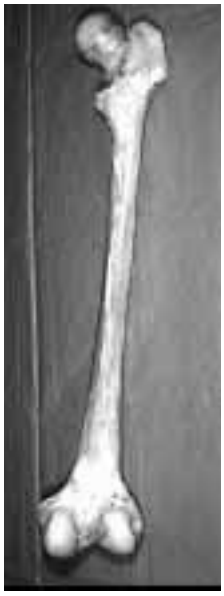


Figure 4: Femoral allograft.

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
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)
1985	AATB Inspection/Accreditation Program initiated 1983
1989	AATB Training and Certification Program for Tissue Bank Specialists (CTBS)
1993	FDA: Interim Rule on Tissue Transplantation (FDA Auditing initiated)
1994	AATB Inspection/Accreditation Program using trained former FDA compliance officers
1997	FDA: Final Rule on Tissue Transplantation
2001	More than 800,000 tissue transplants annually in U.S.
2001	75 AATB Accredited Tissue Banks (Consult AATB Web Site at www.aatb.org)

Figure 5: *First allograft transplantation. 12th Century painting of Saints Cosmos and Damian.*

Figure 6: *AATB Standards.*

Figure 7: Femoral strut.

What has Occurred in Government Regulation?

1984	National Organ Transplant Act
1985	HIV antibody testing (FDA) for blood products
1991	HCV antibody testing (FDA) for blood products
1993	FDA Interim Rule on Tissue Transplantation
1995	JCAHO oversight in tissue banking
1997	FDA: Final Rule on Tissue Transplantation (with guidance)
1997	FDA: Proposed approach to regulation of tissue products
1998	HCFA: Requirements for hospital participation in organ/tissue donation
1999	FDA: Proposed rule suitability determination for donation
2001	FDA: Proposed rule for Good Tissue Practice FDA: Establishment of registration of tissue banks and manufacturers of tissue products
	(1983 to 1998 Public Health Service/Guidance documents)

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 accomplished)

Donor Screening: History

At Time of Donation, **No** History of:

- Recent active infection or sepsis
- Systemic viral illness (Hepatitis, HIV)
- Untreated syphilis, active tuberculosis, leprosy
- Autoimmune disease
- Ingestion toxic substances
- Rheumatoid arthritis, systemic lupus, polyarteritis nodosa, sarcoidosis, myasthenia gravis
- Clinically significant metabolic bone disease
- Clinically significant malignancy
- Dementia, dura mater transplant or use of human derived pituitary growth factor (Spongiform Disease, CJD)
- Risk factors for HIV (as listed by US Public Health Service)

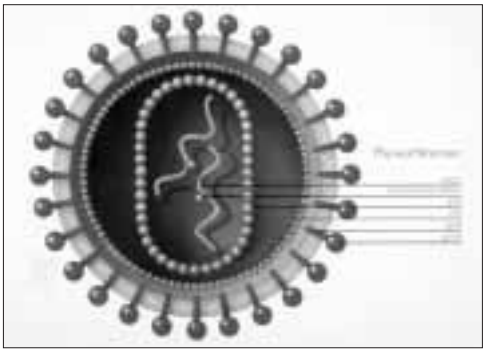


Figure 8: HIV virus - led to improved donor screening.

Donor Screening: Physical Examination

Physical Examination of Potential Donors Includes **No** Evidence of:

- Active infection: viral, bacterial or fungal
- Physical evidence of risk for sexually transmitted diseases such as genital ulcers, herpes simplex, syphilis, chancroid
- Needle tracts (nonmedical); recent tattoos (12 months)
- Lymph node enlargement (disseminated)
- Jaundice, icterus, hepatomegaly
- Blue/purple spots consistent with Kaposi's sarcoma
- Evidence anal intercourse (perianal condyloma)
- Oral thrush
- Open local wounds
- Clinically significant skin lesions

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

	Virus		
	HIV	**HCV**	**HBV**
Window Period using FDA Licensed Tests	22 days (anti $HIV_{1,2}$)	70 days (anti HCV)	56 days (HB_SAg)
Window Period using NAT* Testing	7-12 days**	10-29 days	41-50 days

*Nucleic Acid Test
** p24 testing between 12 and 22 days
Source: Busch MP and Kleinman SH, Transfusion 40:143-146, 2000.

Serologic Testing

Tests Required by FDA; performed by CLIA - approved laboratories:

- HIV 1/HIV 2 Antibody (residual risk 1:689,655)
- HTLV I/HTLV II Antibody
- HB_SAg (residual risk 1:77,220)
- HCV Antibody (residual risk 1:19,850)
- Syphilis
- HB Core Antibody (FDA: For living donors) (general New York State requirement)

Residual Risk Source: GAO/HEHS-98-205 Blood Plasma Safety

Additional Testing Usually Done:

- HIV Antigen
- HIV PCR Testing
- CMV
- Possible use of NAT testing as used in blood

Tissue Processing

- Audited or accredited facility following Good Tissue Practice guidelines
- Validated Quality Control/Quality Assurance Program
- Elimination or reduction of debris and cells to reduce disease transmission
- Bacteriologic and virucidal washes
- Evaluation bacteriologic bioburden (preprocessing cultures to evaluate contamination
- Possible use of gamma radiation 1.2 Mrads (pre- or post-processing)
- Final product testing for bacteriologic contamination (swabs vs. tissue piece)
- Potential discard of tissue or donor lot based on certain types of early bacteriologic contamination
- Final review by tissue bank medical director of screening/serology/processing prior to release of tissue for transplantation

Secondary Sterilization (Selected Tissues)

- Gamma radiation (usually 1.2 Mrads—higher amounts may raise concern for integrity of tissue)
- Ethylene Oxide (concern for residual toxicity and penetration depth)

What are the Episodes of Documented Disease Transmission?

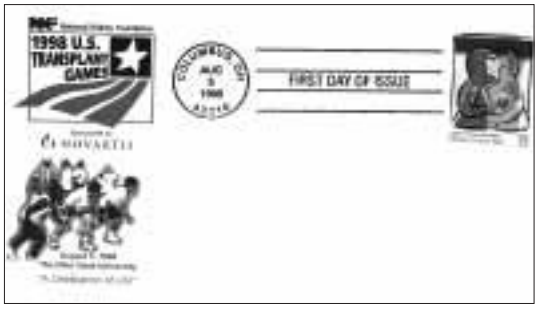
Over past decade more than 4 million musculoskeletal allografts have been safely transplanted. Relatively few incidents of disease transmission have been reported:

Bacterial:

Tuberculosis - One case (four recipients): James et al, JBJS 35B:578, 1953
Infections, miscellaneous:
Three cases: Lord et al, JBJS 70A:369-376, 1988
Five cases currently under investigation by CDC: MMWR Dec. 6, 2001

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
HIV - One Case: MMWR 37:397-99, 1983 (Pre-HIV antibody testing)
Three Cases: Simonds et al, NEJM 326:726-732, 1992 (tissue retrieved 1985)



What is the Message?

- More than 800,000 musculoskeletal allografts distributed in US in 2001
- Disease transmission is very rare
- Conventional sterilization techniques used for metallic implants may adversely affect functional, biological and mechanical properties of most allografts
- No reports of disease transmission using demineralized bone products
- Some grafts can be treated with 1.2 Mrads to reduce contamination
- Inherent safety of the graft is based upon Good Tissue Practices:
    - Donor screening and physical examination
    - Serologic testing
    - Careful processing techniques
    - Attention to quality control/quality assurance
- Need for centralized reporting of adverse episodes by surgeons with subsequent investigation and documentation
- 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