

# Reported infections after human tissue transplantation before and after new food and drug administration (FDA) regulations, United States, 2001 through June, 2010

Tarun K. Mallick · Alexis Mosquera ·  
Craig E. Zinderman · Laura St. Martin ·  
Robert P. Wise

Received: 21 December 2010 / Accepted: 18 March 2011 / Published online: 9 April 2011  
© Springer Science+Business Media B.V.(outside the USA) 2011

**Abstract** Processors distributed about 1.5 million human tissue allografts in the U.S. in 2007. The potential for transmitting infections through allografts concerns clinicians and patients. In 2005, FDA implemented Current Good Tissue Practice (CGTP) rules requiring tissue establishments to report to FDA certain serious infections after allograft transplantations. We describe infection reports following tissue transplants received by FDA from 2005 through June, 2010, and compare reporting before and after implementation of CGTP rules. We identified reports received by FDA from January 2001 through June, 2010, for infections in human tissue recipients, examining the reports by tissue type, organism, time to onset, severity, and reporter characteristics. Among 562 reports, 83 (20.8/year) were received from 2001–2004, before the CGTP rules, 43 in the 2005 transition year, and 436 (96.9/year) from 2006 through June, 2010, after the rules. Tissue processors accounted for 84.2% of reports submitted after the rules,

compared to 26.5% previously. Bacterial infections were the most commonly reported organisms before (64.6%) and after (62.2%) the new rules. Afterward, 2.5% (11) of reports described deaths, and 33.7% (147) involved hospitalizations. Before the rules, 13% (11) described deaths, and another 72% involved hospitalizations. Reports received by the FDA quadrupled since 2005, suggesting that CGTP regulations have contributed to increased reporting and improved tissue safety surveillance. However, these data do not confirm that the reported infections were caused by suspect tissues; most reports may represent routine post-surgical infections not actually due to allografts.

**Keywords** Allografts · Tissue · Infections · Surveillance

## Introduction

Many surgical procedures employ human tissue transplantation. Processors in the U.S. distributed about 1.5 million human tissue allografts in 2007, an estimate that excludes tissue devices, cell therapies, and reproductive tissues (AATB 2010). An additional 54,820 corneas and sclera were distributed in 2007. Historically, transmissions of infection from allograft tissues have been rare, but the potential for disease transmission remains a considerable concern for clinicians and patients. Safety concerns are one of the factors limiting the use of allograft tissue (Vangsnæs et al. 2006).

---

T. K. Mallick · A. Mosquera (✉) ·  
C. E. Zinderman · R. P. Wise  
Office of Biostatistics and Epidemiology,  
FDA/CBER, 1401 Rockville Pike, Suite 400 S,  
Rockville, MD 20852, USA  
e-mail: alexis.mosquera@fda.hhs.gov

L. St. Martin  
Office of Cellular, Tissue, and Gene Therapies,  
FDA/CBER, 1401 Rockville Pike, Suite 200 S,  
Rockville, MD 20852, USA

The U.S. Food and Drug Administration (FDA) began regulating human tissues intended for transplantation in 1993. Those initial regulations pertained to a limited scope of infectious diseases and tissues (21 CFR 1270). On May 25, 2005, FDA implemented new comprehensive rules covering a broad array of human cells, tissues, and cellular and tissue-based products (HCT/Ps) intended for implantation, transplantation, infusion, or transfer into a human recipient (21 CFR 1271) (FDA 2010). These rules apply to tissue establishments that manufacture HCT/Ps (i.e., recover, process, store, label, package, or distribute tissue, or screen or test donors). They address screening and testing of potential donors, and current good tissue practice (CGTP). Donor screening includes a donor medical history interview; physical assessment or examination; and review of available relevant medical records for risk factors for, or clinical evidence of communicable diseases. Donor testing looks for HIV, viral hepatitis, and other specific communicable diseases. CGTP includes measures designed to ensure that tissues are not contaminated and do not become contaminated during manufacturing. Such measures include facility cleaning and sanitation; environmental controls and monitoring; and testing of tissues for microorganisms, or use of methods validated to reduce or remove them. These measures provide redundant layers of safety assurance; however, failures in processing could lead to transmission of infections by tissues.

Under the CGTP rules, a tissue establishment must investigate any “adverse reaction,” defined as a “noxious and unintended response to a tissue or cell product for which there is a reasonable possibility that the product caused the response” (FDA 2005). Tissue establishments must report to FDA serious adverse reactions involving communicable diseases. Prior to 2005, reporting of adverse events associated with most tissue products was voluntary. Heart valves and dura mater, however, were regulated until May 25, 2005 as devices, and manufacturers were required to report adverse events for these products to FDA’s Center for Devices and Radiologic Health (CDRH).

The objectives of this study were to describe reports received by FDA for infections following tissue allograft transplantation and to identify trends in tissue types (e.g., bone, musculoskeletal soft tissue, skin, or cornea), infecting organism, or other report characteristics that might point to possible safety issues

associated with allograft use. Wang, et al. described reports to FDA for infections after tissue transplantation from 2001 through 2004, prior to implementation of the new tissue rule (Wang et al. 2007). We now describe reports received by FDA between 2005 and June, 2010, and compare reporting before and after implementation of the new rules. We hypothesized that the regulations would result in a marked increase in the frequency of reported infections submitted to FDA, improving tissue safety through increased ascertainment of potentially allograft-attributable infections and related information, such as product types, indications for use, and donor risk factors that could be associated with recipient infections.

A variety of bacterial and viral infections following implantation of human bones, musculoskeletal soft tissues, skin, cornea, and heart valves have been reported to the Centers for Disease Control and Prevention (CDC). Reported organisms have included *staphylococcus*, *streptococcus*, *clostridium*, HIV, HCV, and rabies (Centers for Disease Control 1988, CDC 2001, 2002, 2003a, 2003b). Transmission of Creutzfeldt-Jakob disease has been associated with transplants of cornea and dura mater (Lang et al. 1998, Maddox et al. 2008). A widespread recall of tissues in 2005 from a tissue recovery firm that had not followed FDA-required procedures for donor screening and testing sparked new concerns about tissue safety (CDC 2006). CDC hosted a 2005 workshop on organ and tissue allograft safety to share information and discuss challenges. The participants proposed that clues of allograft associated infections might include unexpected pathogens, allograft removal due to infection, and hospitalization for infection (CDC 2005).

Disease transmissions through allografts can stem from an infected donor or tissue contamination during procurement or processing. In 2006, a tissue bank attributed knee infections with *Elizabethkingia meningoseptica*, previously *Chryseobacterium meningosepticum*, in two allograft recipients from different donors to contamination at its processing facility. The firm voluntarily recalled over 4,700 tissues that had been processed at the facility (Cartwright et al. 2010).

## Methods

We reviewed adverse reaction reports to FDA for infections after tissue transplant. This case series

describes infections that followed but were not necessarily due to allograft transplantation. We identified all reports for HCT/Ps received from January 1, 2001 through June 30, 2010, including reports submitted before and after the implementation of the CGTP rules. MedWatch, FDA's safety information and adverse event reporting program, receives reports for HCT/Ps from various sources, including tissue establishments, health care providers, and consumers. Reports can also be submitted through FDA's Medical Product Surveillance Network (MedSun), an enhanced surveillance program for device-related safety information, which includes a tissue surveillance component (FDA 2009). Data from 2001–2004, prior to the new rules, have appeared previously and provide the basis for our comparison to the period since 2006, after they took effect. We treat 2005 as a transitional year.

We defined a case as a reported infection with onset after allograft implantation, identifying an HCT/P as the suspect product, and received by FDA between January 1, 2001, and June 30, 2010. HCT/Ps include bone, tendon, skin, dura mater, heart valve, and cornea. We excluded cells and cellular-based products from this review, because cells are fundamentally different from tissues and usually used in patients with severe systemic illnesses and immunosuppression. Cells receive minimal anti-infective processing and the risk factors for and rates of post-transplant infections would differ in recipients of these products. Our review also excludes adverse reaction reports for animal-derived cells, tissues, and organs, which FDA regulates as devices or as xenotransplantation products, as well as reports for human organ transplants, which are overseen by the Health Resources and Services Administration.

The time to onset is the interval between allograft implantation and the diagnosis of infection if available. If date of diagnosis was not provided, we used the earliest date of antibiotic use or other intervention for the infection. Seriousness of infections was coded as death, hospitalization, and/or other interventions. If reported, infectious organism(s) were classified as bacterial, fungal, or viral.

## Results

During the overall period from 2001 through June, 2010, 562 reports met the case definition, 83 (20.8 per

**Table 1** Infection reports by year

Year	Reports	Percentage
2001	7	1.2
2002	41	7.3
2003	20	3.6
2004	15	2.7
2005	43	7.7
2006	96	17.1
2007	90	16.0
2008	88	15.7
2009	116	20.6
2010*	46	8.2
Total	562	100.0

\* Data through June, 2010

year) from 2001–2004, before the new rules, 43 in the 2005 transition year, and 436 (96.9 per year) in the 4.5 years from 2006 through June, 2010 (Table 1). The peak in 2002 reflects a large recall of all musculoskeletal soft tissues from one processor whose practices had contributed to contamination (FDA 2002, Kainer et al. 2004). This firm accounted for 75% of reports from 2002 (Wang et al. 2007).

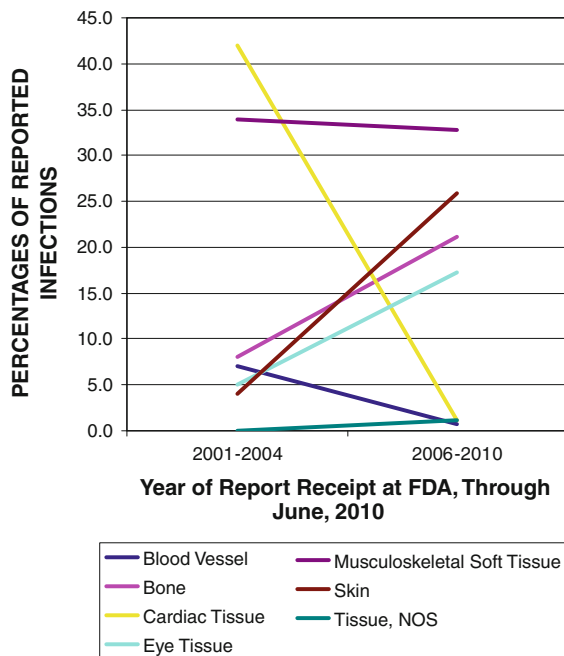
From 2006 through June, 2010, manufacturers submitted 367 (84.2%) of the reports, while physicians or others submitted 79 reports to FDA directly, or 18.1% of the total. (Because FDA received 10 reports from manufacturers as well as directly from physicians or others, these percentages are not additive.) In the 2001–2004 period, manufacturers provided a much smaller fraction of reports (26.5%).

### Tissue allograft types

Musculoskeletal, skin and bone grafts accounted for the largest fraction of reports from 2006 through June, 2010, while cardiac tissues and blood vessels accounted for relatively few reports (Fig. 1). Cardiac valves accounted for 42 percent of reports in the 2001–2004 period versus only 1.1% from 2006 through June, 2010.

### Identified organisms

Among 436 reports with specific organisms or infection types from 2006 through June, 2010, bacteria accounted for the majority (271, or 62.2%,



**Fig. 1** Graft types in reports of infections before and after new regulations

including two patients with both bacterial and fungal infections), as in the earlier period, before the new regulations (64.6%) (Table 2). *Staphylococcal aureus* infections in 73 reports included 37 patients with unspecified *S. aureus*, 31 *methicillin resistant (MRSA)* infections, and 5 *methicillin sensitive (MSSA)*. Another 39 reports described coagulase negative staphylococcal infections.

Fungal infections were reported in 36 reports (including the two mixed infections), a smaller fraction of the more recent reports than of the earlier

**Table 2** Infectious disease classes before and after new reporting regulations

Organisms	2001–2004*		2006–June, 2010	
	No.	%	No.	%
Bacteria**	42	64.6	271	62.2
Fungi**	25	38.5	36	8.3
Virus	0	0.0	48	11.0
Prion	1	1.5	6	1.4
Unknown	18	27.7	77	17.7
Total	65	100.0	436	100.0

\* Data based on Wang et al. 2007

\*\* Two reports described bacterial as well as fungal infections during 2006–June, 2010

ones (8.3% vs. 38.5% earlier). In 48 reports between 2006 and June, 2010 (11.0%) viral infections included hepatitis C (HCV, 25 cases, including one with hepatitis B and one with HIV), hepatitis B (9, including one with HCV), herpes simplex virus (7), HIV (6, including 2 with HCV), and one report each for cytomegalovirus, hepatitis A, and human T-lymphotropic virus I/II. Wang et al. found no viral infection reports between 2001 and 2004.

#### Time to infection

We evaluated 114 reports in the 2006–June, 2010 period with adequate information on the interval from implantation until first evidence of an infection. Bacteria accounted for 85 reports (in addition to one with fungal infection, as well), with post-implantation intervals ranging from 0 to 356 days and a median of 14 days. Fungal infections in 15 reports (in addition to the combined infection case) had onset intervals as long as 197 days, with a median of 49 days. Viral infections in 11 reports had onset intervals up to 7 years, with a median of 24 days. Wang et al. described somewhat longer median intervals in the 2001–2004 period for bacterial (1 month) and fungal infections (3 months).

#### Reported deaths

Patients had expired in 11 reports (2.5%) from 2006–June, 2010 (Table 3). Six identified Creutzfeldt-Jakob disease (CJD). None of these could be definitively attributed to transmission by the tissue product and could represent sporadic CJD. Three of the 6 involved corneas, and one involved dura mater; both of these products have previously been implicated in CJD transmissions, although corneal associations may also arise from sporadic CJD (Maddox et al., and Blossom et al. 2007). The report of CJD after implantation of bone tissue, which has not been recognized thus far as a vehicle for transmission of prion infection, describes a patient with dementia that may have preceded the allograft procedure. The patient's confusion and declining mental status had emerged within 1 week afterward, and there was no autopsy confirmation of the diagnosis. Expert review at FDA and CDC concluded that this report does not represent probable or confirmed CJD transmission from bone tissue. Another patient received

**Table 3** Reported deaths, 2006–June, 2010

Year	Reported organism	Tissue type
2006	CJD	Cornea
2007	Escherichia coli, Klebsiella oxytoca, Staphylococcus epidermidis, and Stenotrophomonas maltophilia	Skin tissue
2007	CJD	Tissue, NOS
2007	Unknown	Tissue, NOS
2008	Pseudomonas fluorescens	Cardiac tissue
2008	CJD	Bone tissue
2008	CJD	Cornea
2008	CJD	Musculoskeletal soft Tissue
2009	Methicillin-resistant Staphylococcus aureus	Bone tissue
2009	CJD	Cornea
2010*	Unknown	Musculoskeletal soft tissue

\* Data through June, 2010

musculoskeletal soft tissue for a rotator cuff repair. He expired some 9 months later after a clinical course that his neurologist felt was consistent with CJD. This tissue recipient also had no autopsy to confirm the diagnosis. The donor of the graft had no risk factor for CJD and negative prion antibody studies of brain tissue. From 2001–2004, 11 reports (13%) described fatalities. Eight of these 11 deaths involved heart valves from the processor that recalled tissues in 2002.

#### Hospitalizations and interventions

Hospitalization in 147 cases (33.7%) was proportionally much less frequently reported in 2006–June, 2010 than before the new regulations (72%). Patients in a modestly smaller fraction of the more recent reports required interventions, such as antibiotic therapy, arthroscopy, incision and drainage, graft removal, or other procedures (208 reports, or 47.7% vs. 59% in the 2001–2004 period).

#### Discussion

Contaminated allografts can pose significant public health and safety concerns and result in severe health consequences for recipients. In the first few years following implementation of the new CGTP Regulations, increasing numbers of possible infectious

transmissions from HCT/Ps have been reported to FDA. Close surveillance of these reports provides potential for early recognition of infectious disease transmissions and interdiction of additional implantations from an implicated source. However, it is essential to recognize that these anecdotal case reports represent suspected but unconfirmed allograft infectious transmissions; post-operative infections in tissue recipients are probably most often due to the same causes as post-operative infections in other settings, rather than actually being attributable to the allograft.

Our analysis encompassed reports received by FDA before and after new reporting regulations took effect in May, 2005. These rules require tissue manufacturers to report infections to FDA if they seem reasonably possible to have been caused by an HCT/P made available for distribution, and if:

1. Fatal
2. Life-threatening
3. Result in permanent impairment of a body function or permanent damage to body structure; or
4. Necessitate medical or surgical intervention, including hospitalization

Generally healthy patients commonly receive allografts in such settings as orthopedic reconstructions after athletic injuries. Although our data do not systematically track underlying conditions, we recognized factors in many reports that would increase a

patient's vulnerability to infection, such as reconstructions after breast cancer. In addition, many corneal transplant recipients are elderly. It is important, however, to appreciate that this collection of case reports provides no basis for prospective estimation of infection risks (incidence rates) associated with allograft implantations. On the other hand, the distribution of organism types may provide guidance for further research and clinical vigilance, such as the importance of suspecting fungal infection in a patient with infectious signs or symptoms and no other explanation, even many weeks after an allograft implantation.

A limitation in our analysis is that we tabulated reports by date of receipt at FDA. Even regarding 2005 as a transition year, our earlier and later reporting periods do not correspond precisely with the legal implementation of the new regulations. They apply to tissues recovered on or after May 25, 2005; some tissues recovered prior to that date would have a long shelf life and likely be implanted much later. On the other hand, the reporting behavior of tissue processors may have converted more uniformly to the new procedures on this date, regardless of each tissue's recovery date.

This review generally followed procedures employed for the earlier period by Wang et al. however we included reports with intervals > 1 year between an allograft's implantation and recognition of infection. This change had little impact, since only two cases, both viral infection reports, had intervals longer than 1 year.

Prior to the new regulations, reports for tissue allografts were submitted voluntarily by manufacturers, health care professionals, and consumers. In contrast, after the regulations took effect, the majority of reports were mandatory submissions from tissue manufacturers. Although there was an overall increase in infection reports received annually, the more than tripling in the manufacturer fraction of these reports (26.5% between 2001 and 2004 vs. 84.2% from 2006–June, 2010) suggests that the increase reflects tissue manufacturers' awareness of and compliance with the new FDA regulations. We cannot estimate the contribution due to the Joint Commission's standard issued in 2005 requiring accredited hospitals to report adverse events to tissue suppliers, but it may also have contributed to these increases (Joint Commission 2010).

The relatively high fraction of all reports associated with cardiac tissues in the 2001–2004 period might only reflect stimulation of reporting from publicity associated with the large recall in 2002. FDA's public health notification regarding this recall included this language: "Even though FDA has not included allograft heart valves in the FDA recall order ..., FDA still has serious concerns regarding the processing and handling of allograft heart valves by Cryolife because patients who receive these devices may be at increased risk for infection" (FDA 2002). Except for cardiac tissues, the actual numbers of reports received for all graft types increased in the 2006–June, 2010 period.

The higher proportion of fungal infection reports submitted before the new regulations might reflect an inclination for health care practitioners to voluntarily report infections with unusual or unfamiliar organisms like fungi.

FDA's monitoring of tissue adverse reaction reports has limitations that are intrinsic to passive safety surveillance for all medical products. Duplicate reports can arise when multiple reporters describe the same patient's experience. However, in this analysis, with substantial clinical information usually examined, we believe that undetected duplications would be very few if any.

Under-reporting is typical in passive surveillance systems, generally recognized to be extensive but usually impossible to quantify. The actual number of infections that follow tissue transplantations is probably higher than the 562 reported before and after the new regulations. The inability of passive surveillance systems to capture all incident events may be influenced by numerous factors, including publicity and perceptions of the transplanting community regarding product safety (Strom and Tugwell 1990, Chen et al. 1994). True tissue infections may be assumed to be expected post-surgical site infections and not reported, especially when the organisms involved are common in this setting. In addition, adverse events in recipients of tissues transplanted with devices (such as screws to fasten allograft ligaments) may be reported with the device as the suspect product, rather than the tissue product. On the other hand, the Joint Commission's standard for hospital reporting of adverse events to tissue suppliers may have increased the completeness of primary reporting from the hospitals to the processors

(Joint Commission 2010). Overall, we assume that this case series represents only a subset of actual post-implantation infections possibly caused by allograft transmissions, and we emphasize that the reported infections provide no basis for estimating actual incidence rates. Not all reported infections are likely to have been actually transmitted by the identified allograft, as illustrated by the implausibly short interval after implantation in numerous reports of infection with bacteria (8 cases), viruses (5), and fungi (1) within the first day after surgery. Many infections with longer intervals might also have been only coincidentally related to allograft implantations, and actually contracted like any other surgical wound infection from skin or other contamination, rather than from the implanted graft.

Many reported allograft associated infections had serious sequelae, including death. The proportion of reports, both prior to and after the new regulations, indicating hospitalization and intervention was greater than the proportion identifying only antibiotic use. This finding is not surprising, because under current rules manufacturers are only required to submit certain serious reports to FDA. Thus, the proportion of serious infections in our data may differ greatly from the actual spectrum of post-implantation infections.

Assessment of whether an implanted graft has caused an infection is often difficult or impossible, since many factors can contribute, such as contamination of the surgical site or a patient's impaired immune system. Many reported infections are unlikely to be due to the graft. The reported infections that we reviewed involved multiple tissue types and a variety of organisms, many of which are common nosocomial organisms. If a culture identifies an unusual and unexpected organism, it may provide a clue to possible allograft transmission. However, infections with organisms common among postoperative patients may often escaped detection. Tissue establishments monitor reports of infections in recipients and may detect other clues to possible allograft transmission, including: two or more similar infections identified in recipients of tissue products from a single donor; and correspondence between an organism identified in a recipient's infection and results of cultures from the donor's tissues (recovery, pre- or post-processing cultures performed by a tissue recovery firm or tissue processor).

Still, there are important limitations to current safety surveillance for tissue allografts which may be

minimized through efforts underway to create a comprehensive national biovigilance program to enhance adverse event monitoring, and facilitate quality assurance and emerging threat assessment. A 2009 Public Health Service review (PHS 2009) highlighted several gaps in tissue, organ, and blood safety, and made recommendations for a public-private partnership in biovigilance. Some of the gaps in allograft surveillance were: limited information on the potential for tissue allografts to transmit infectious disease; limited ability to ascertain whether a reported infection in a tissue allograft recipient was transmitted by the tissue; no regulatory requirement for hospitals and healthcare providers to report adverse reactions experienced by their patients; limited tracking of tissues to the level of the recipient; and lack of a nationwide organ/tissue donor network with a common donor identifier for linkage of organs and tissues from the same donor. The CDC completed a pilot project in 2008 for a Transplantation Transmission Sentinel Network ([http://www.cdc.gov/ncidod/dhqp/pdf/hicpac/DHQP\\_HICPACnov08presentation.pdf](http://www.cdc.gov/ncidod/dhqp/pdf/hicpac/DHQP_HICPACnov08presentation.pdf)). This pilot envisioned a centralized system for registering implantations and subsequent infections based on clinical symptoms and laboratory evidence (Strong et al. 2010, Joyce et al. 2010). The pilot also employed a universal donor identification number that would allow tissue establishments or Federal agencies to link possible infections in organ and tissue recipients to a common donor. A biovigilance program that incorporated these elements could detect clusters of infections associated with a common donor or tissue establishment and allow faster interdiction through better traceability to the donor.

We did not identify clustering of infections with any particular tissue type or organism. Bacteria were the most commonly reported class of infectious agents in the past and under the new regulations, followed by fungal infections. Because of the long incubation period of fungal organisms relative to bacterial organisms, health care practitioners should consider the possibility of a contaminated allograft when a fungal infection follows an allograft implantation after intervals as long as a month or more. The median time from implantation to infection in reports involving fungal organisms was long (49 days). However, we can not draw conclusions regarding onset interval from these reports alone because the attributability to the allografts is unknown.

The quadrupling of reports received by FDA since 2005, from an average of 20 reports per year to 97 reports per year, is consistent with a hypothesis that the new regulations regarding tissue manufacturing and adverse reaction reporting have contributed to increased reporting, thus improving tissue safety surveillance. With voluntary reporting before the regulations, health care practitioners and consumers may have been more likely to report only events that were particularly unusual (e.g., infections with organisms rarely identified in otherwise healthy patients) or events with an unusually serious outcome, such as deaths. With mandatory reporting, any serious infection with a reasonable possibility to be caused by the tissue should be reported, potentially decreasing the effect of reporting bias.

FDA continues to monitor adverse reactions associated with tissue allografts through the Med-Watch surveillance system. Reports can be submitted by phone (1-800-638-2041), fax, mail, or the internet ([www.fda.gov/medwatch](http://www.fda.gov/medwatch)).

**Acknowledgments** The authors appreciate Alan Ou, M.D., M.P.H. and Ellen Lazarus, M.D. for their review of an advanced draft of this work and several useful suggestions.

## References

- American Association of Tissue Banks (2010) 2007 American association of tissue banks (AATB) annual survey of accredited tissue banks in the United States. McLean, VA Blossom DB, Maddox RA, Beavers SF, Church KA, Thoroughman DA, Schonberger LB, Belay ED (2007) A case of Creutzfeldt-Jakob disease associated with a dura mater graft in the United States. *Infect Control Hosp Epidemiol* 28(12):1396–1397
- Cartwright EJ, Prabhu RM, Zinderman CE, Schobert WE, Jensen B, Noble-Wang J, Church K, Welsh C, Kuehnert M, Burke TL, Srinivasan A, Food and Drug Administration Tissue Safety Team Investigators (2010) Transmission of Elizabethkingia meningoseptica (formerly Chryseobacterium meningosepticum) to tissue-allograft recipients: a report of two cases. *J Bone Joint Surg Am* 92(6):1501–1506
- Centers for Disease Control (1988) Transmission of HIV through bone transplantation: case report and public health recommendations. *MMWR Morb Mortal Wkly Rep* 37(39):597–599 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/00001284.htm>, accessed October 28, 2010)
- Centers for Disease Control, Prevention (2001) Septic arthritis following anterior cruciate ligament reconstruction using tendon allografts—Florida, Louisiana, 2001. *MMWR Morb Mortal Wkly Rep* 50(48):1081–1083
- Centers for Disease Control, Prevention (2002) Update: allograft-associated bacterial infections—United States, 2002. *MMWR Morb Mortal Wkly Rep* 51(10):207–210
- Centers for Disease Control and Prevention (2003a) Invasive Streptococcus pyogenes after allograft implantation—Colorado, 2003. *MMWR Morb Mortal Wkly Rep* 52(48):1174–1176
- Centers for Disease Control and Prevention (2003b) Hepatitis C virus transmission from an antibody-negative organ and tissue donor—United States, 2000–2002. *MMWR Morb Mortal Wkly Rep* 52(13):273–276
- Centers for Disease Control and Prevention, Food and Drug Administration, and Health Resources and Services Administration, Department of Health and Human Services (2005) Workshop on preventing organ and tissue allograft-transmitted infection: priorities for public health intervention. 2005 June 2–3. [http://www.cdc.gov/ncidod/dhqp/pdf/bbp/organ\\_tissueWorkshop\\_June2005.pdf](http://www.cdc.gov/ncidod/dhqp/pdf/bbp/organ_tissueWorkshop_June2005.pdf) Accessed 2011 March 15
- Centers for Disease Control, Prevention (2006) Brief report: investigation into recalled human tissue for transplantation—United States, 2005–2006. *MMWR Morb Mortal Wkly Rep* 55(20):564–566
- Chen RT, Rastogi SC, Mullen JR, Hayes S, Cochi SL, Donlon JA, Wassilak SG (1994) The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 12:542–550
- Food and Drug Administration (2002) Public health web notification: Human tissue processed by Cryolife, Inc. (<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM064529>, accessed October 28, 2010)
- Food and Drug Administration (2005) Guidance for industry: MedWatch Form FDA 3500A: Mandatory Reporting of adverse reactions related to human cells, tissues, and cellular and tissue-based products (HCT/Ps) (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm074000.htm>, accessed October 28, 2010)
- Food and Drug Administration (2009) MedSun: Medical product safety network (<http://www.fda.gov/MedicalDevices/Safety/MedSunMedicalProductSafetyNetwork/default.htm>, accessed October 28, 2010)
- Food and Drug Administration (2010) 21 CFR 1270.150, Current good tissue practice requirements (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ActsRulesRegulations/TissueProposedFinalRules/default.htm>)
- Joint Commission (2010) Standards TS.03.01.01-TS.03.03.01 (<http://www.lpitsolutions.com/support/complianceresources.aspx>, accessed March 17 2011)
- Joyce M, Strong DM, Brubaker S, Mroz TE (2010) Tracking and tracing of allograft tissue based on a common universal donor number are lacking: progress and obstacles on a transplantation transmission sentinel network (TTSN). *US Musculoskeletal Review* 2010; 5: 36–8
- Kainer MA, Linden JV, Whaley DN, Holmes HT, Jarvis WR, Jernigan DB, Archibald LK (2004) Clostridium infections associated with musculoskeletal-tissue allografts. *N Engl J Med* 350(25):2564–2571
- Lang CJ, Heckmann JG, Neundörfer B (1998) Creutzfeldt-Jakob disease via dural and corneal transplants. *J Neurol Sci* 160(2):128–139
- Maddox RA, Belay ED, Curns AT, Zou WQ, Nowicki S, Lembach RG, Geschwind MD, Haman A, Shinozaki N,



- Nakamura Y, Borer MJ, Schonberger LB (2008) Creutzfeldt-Jakob disease in recipients of corneal transplants. *Cornea* 27(7):851–854
- Public Health Service Biovigilance Task Group (2009) Biovigilance in the United States: efforts to bridge a critical gap in patient safety and donor health. ([http://www.hhs.gov/ash/bloodsafety/biovigilance/ash\\_to\\_acbsa\\_oct\\_2009.pdf](http://www.hhs.gov/ash/bloodsafety/biovigilance/ash_to_acbsa_oct_2009.pdf), accessed December 15, 2010)
- Strom BL, Tugwell P (1990) Pharmacoepidemiology: current status, prospects, and problems. *Ann Intern Med* 113(3): 179–181
- Strong DM, Seem D, Taylor G, Parker J, Stewart D, Kuehnert MJ (2010) Development of a transplantation transmission sentinel network to improve safety and traceability of organ and tissues. *Cell Tissue Bank*, 2010 Jul 21
- Vangsnest CT Jr, Wagner PP, Moore TM, Roberts MR (2006) Overview of safety issues concerning the preparation and processing of soft-tissue allografts. *Arthroscopy* 22(12): 1351–1358
- Wang S, Zinderman C, Wise R, Braun M (2007) Infections and human tissue transplants: review of FDA MedWatch reports 2001–2004. *Cell Tissue Bank* 8:211–219