AATB’s Report: Adverse Reporting Systems & Requirements

TTSN Organ & Tissue Safety Workshop
June 5, 2007
Reston, Virginia

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Current Practices

• Adverse event/reaction/outcome reporting requirements
  ❖ Federal, State, International
  ❖ AATB Standards & Accreditation Policy
  ❖ Investigation Practices - Flowchart

• Definitions
  ❖ Possible, Probable, Proven, Indeterminate, or Excluded

• Implant Card Experience Tracking
Reporting Requirements

• Federal - refer to Melissa’s excellent presentation!

• State

  ❖ **New York** - *Title 10 NYCRR Part 52; and subparts 52-2 Licensure, 52-3 General Technical*

  ◦ Covers tissue banks & transplant centers

  ◦ Adverse outcome reporting & records required for transplant centers

  ◦ Required reporting by tissue banks (within 7 calendar days) of “Errors and Accidents” if grafts distributed; relates to reporting above by transplant center

  ◦ Must submit annual activity reports (provides denominator)
Reporting Requirements

- **State (continued)**
  - **Florida (AHCA)**
    - Requires tissue bank to report ALL potential adverse reactions using Part I of Adverse Reaction Report
      - Only required when the report is made to the tissue bank by the transplanting physician or hospital
      - Required within one working day
    - After investigation by tissue bank, then requires reporting using Part II of Adverse Reaction Report
      - Required when investigation concluded
    - AHCA not involved in investigations
Reporting Requirements

• International
  ❖ Canada
    ○ Proposed CTO Regulations
      ✴ Report all adverse reactions within 24 hrs to Health Canada and provide updates every 30 days
  ❖ Medical Device Reporting Schemes
    ○ EU Authorities - Medical Device Vigilance
    ○ Canada - Therapeutic Products Program
    ○ Australia - Therapeutic Goods Act
    ○ Japan - Adverse Reaction Reporting
AATB Standards

• **1984 (1st Edition)** - must maintain an adverse reaction file; recall procedures must exist

• **1993 (6th edition)** - new standards for “Medical Facility Tissue Storage and Issuance” requires adverse outcome reporting to tissue bank & recall procedures must be written
AATB Standards

- **1996** (7th edition) - requires Tissue Distribution Intermediaries to investigate & report adverse outcomes to tissue bank & to have recall procedures

- **1998** (8th edition) - tissue bank “shall establish recipient follow-up collection protocols”
  - Implant cards most often used
AATB Standards

In A2.000 Definitions of Terms:

ADVERSE OUTCOME - An undesirable effect or untoward complication in a recipient consequent to or reasonably related to cells and/or tissue transplantation.
AATB Standards

In A2.000 Definitions of Terms:

**ERROR** - A departure, whether or not intentional, from the SOPM, standards, or applicable federal, state, and/or local laws and/or regulations during donor screening, testing, retrieval, processing, quarantine, labeling, storage, distribution, or dispensing of cells and/or tissues that may cause infectious disease transmission, adversely affect the clinical performance of cells and/or tissue, and/or interfere with the ability to trace cells and/or tissue to the donor.
The Medical Director shall establish policies and procedures regarding Adverse Outcomes and shall require that all potential Adverse Outcomes are investigated and documented. Corrective actions shall also be documented. All final summary reports shall be reviewed and approved by the Medical Director. Adverse Outcomes must be reported as required by applicable federal, state and/or local laws and/or regulations.
G3.000 Labeling Information
G3.210 Package Insert Content
  11) Statement that Adverse Outcomes potentially attributable to the cells and/or tissue must be reported promptly to the tissue supplier

H5.000 Recalls - General
H5.400 Recalls of Transplanted Tissue
  .....shall be handled as a potential Adverse Outcome investigation...
J1.000 Standard Operating Procedures Manual (SOPM)

J1.200 Contents

6) Quality Assurance and Quality Control.....
   b) Policies and procedures for the investigation, documentation, and reporting of Accidents, Errors, Complaints, and Adverse Outcomes (Ref. Section K4.000);

J1.600 Annual Review
The Director or designee shall perform and document an annual review of all policies and procedures. The Medical Director shall perform and document an annual review of the SOPs for Donor suitability and Adverse Outcomes.
AATB Standards

**K1.000 QUALITY ASSURANCE PROGRAM**

**K4.000 INVESTIGATIONS**

The QA Program shall provide for the completion of the investigation of Accidents, Errors, Complaints, and Adverse Outcomes. The QA Program, in conjunction with the Director or Medical Director, shall approve corrective actions prior to implementation. Precipitating events, recommendations, and Resolutions shall be documented in a summary report by the staff involved and reviewed for completeness and Resolution by the QA Program. All reports generated shall be retained on file for 10 years.
K4.200 Complaints

All written and oral Complaints regarding cells and/or tissue quality, Safety, packaging, or effectiveness shall be investigated to determine whether the Complaint is related to an Error, Accident, Adverse Outcome, or other factor. Each investigation shall determine whether associated cells and/or tissue may be affected. If it is determined that they may be affected, those associated cells and/or tissue shall be located and Quarantined until Resolution of the incident (which may involve initiation of a Recall). Complaints that are medical in nature shall be reviewed by the Medical Director or licensed physician designee.
AATB Standards

K1.000 QUALITY ASSURANCE PROGRAM
K4.300 Adverse Outcomes

All reported or suspected Adverse Outcomes that are potentially related, directly or indirectly to an Allograft shall be investigated thoroughly and expeditiously. The Medical Director or licensed physician designee shall review all potential Adverse Outcome reports and be involved in determination of the impact and Resolution of any Adverse Outcome. If investigation indicates that the Adverse Outcome is related to an Error or Accident, then procedures for Error and Accidents (K4.100) shall also be followed.
In accordance with applicable federal, state, and local regulations, confirmed cases of transmissible disease in a Recipient attributed to cells and/or tissue transplantation shall be reported in writing in a timely fashion to public health authorities, organ retrieval organizations and Tissue Banks involved in any manner with cells and/or tissue retrieved from the same donor and the physician(s) involved in the transplantation of cells and/or tissue from that donor. Notifications shall be documented in the donor’s record.
AATB Standards

Section L - Tissue Dispensing Services
L5.000 ADVERSE OUTCOMES
Potential adverse reactions, suspected transmission of disease, or other complications, directly or indirectly related to the Allograft, shall be reported to the tissue processor and thoroughly investigated and documented.

Section M - Tissue Distribution Intermediary
M8.000 ADVERSE OUTCOMES
Reports of Adverse Outcomes, transmitted disease, or other complications shall be reported to the supplier of the cells and/or tissue in a timely fashion and in accordance with applicable federal, state, and/or local laws and/or regulations.
Since August 2004

❖ Required reporting to AATB Executive Office of “Reportable Contrary Events”

○ Federal, state, or local actions:
  ✴ Warning Letters, recall notices, licensure change

○ Recalls - voluntary or otherwise

○ Confirmed Adverse Events - contamination or disease
Begin: Receive report of suspected allograft transmitted infection

- Adverse Event form/database entry (note: not every action outline is applied but this symbol is not required

Communicate to Responsible Person of RA/IA

Communicate to Medical Director

Return Graft Authentication Form

Review report for tracking of complaints to determine recall status, may require additional investigation or notification

Determine Reporting Requirements

MDR Scheme; Internation Communications

MedWatch entry form

**EUV (MDV), Canada (TPP, Australia (TPA), Japan (ADD)

- Determine if "probable" allograft transmitted infection

- Voluntary market withdrawal or recall may be initiated

Determine if "probable" allograft transmitted infection

Yes

No

Review decision: HS, produce summary report

- Enter into appropriate adverse event database and initiate Responsible Person actions

CAPA - Inprocess test/impact

- Determine if "probable" allograft transmitted infection

A. Pre-processing, inprocessing, post-processing culture results, Resent, equipment, and material records, Environmental monitoring test results

B. Donor: Medical Hx, clinical course, CEDO, autopsy, all cultures, lab work, functional assessment

Recipient: current clinical course, lab work/cultures, operative report

C. Clinical course, symptoms, all cultures/tests, operative report, how graft culture was obtained or implant, viral testing bx

D. Recovery Agency, other

Contract Processing Agencies, FDA, CDC, NTDH, FL, others; AAM, ASABE, appropriate state/county health dept., International if applicable**
“Possible/Suspected” definition

Begin: Receive report of suspected allograft-transmitted infection

Adverse Event form/database entry (note: w/ every action rectangle this applies but this symbol is not repeated)

Enter into appropriate adverse event database and contact Responsible Persons

Communicated to Responsible Person of RA/QA

Communicated to Medical Director

Regulatory Affairs/Quality Assurance

Medical Director

Two pathways taken during investigation
Regulatory/QA Pathway

A. Pre-processing, in-processing, post-processing culture results. Reagent, equipment, and material records. Environmental monitoring test results

Communicated to Responsible Person of RA/OA

- Return Graft Authorization form
- Quarantine Graft form/database designation
- In-house Donor Record

Review report information, assign event-tracking code, check for other complaints involving same donor, ensure any returned grafts are quarantined; quarantine inventory not yet distributed or released, verify w/reporting entity that complaint was received and investigation in process, review donor chart (A.)

Other complaint report(s) exist(s) for this donor

Determine product type affected by adverse report

(Affects) 351 products
(Affects) 361 products
Medical Director Pathway

B. Donor: Medical Hx, clinical course, COD, autopsy, all cultures, lab work, trauma/physical assessment. Recipient: current clinical course, lab work/cultures, operative report

C. Clinical course, symptoms, all cultures/tests, operative report, how graft culture was obtained at implant, viral testing hx

Communicated to Medical Director

Review report information and in-house donor record (B.)

Communicate with recipient’s physician (or reporting person)

Request specific recipient information/medical records (C.)

Review information received

Determination whether or not this is a “possible” allograft-transmitted infection. MUST be done w/in 15 days of initial report, regardless of delays*

Delayed or no response to requests*

All known information is

MedWatch entry/form.
“Probable” definition

- Determine Reporting Requirements
- MedWatch entry/form
- MDR Scheme; International Communications
  - **EU (MDV), Canada (TPP), Australia (TFA), Japan (ARR)**
- Actions for Responsible Person of RA/OA
- FDA and/or CDC Investigation
- **D. Recovery Agency, other Contract Processing Agency(ies), FDA, CDC, NYDOH, Florida AHAC, AATB, appropriate state/county health dept., International if applicable**
- Institute formal recall
- Immediately Contact Appropriate Agencies (D.)
- Voluntary market withdrawal (or recall) may be instituted
- Enter into appropriate adverse event database and initiate Responsible Person actions
- Request specific recipient information/medical records and/or samples
- Delayed or no response to requests
- Test recipient samples
- Close Report
- Communicate with original reporting entity
- Review decision Hx, produce summary report
- Yes
- No

RA/QA Contacts
Appropriate Entities

“Excluded” definition needed
“Proven” definition

“Indeterminate” definition needed
Will solicit support from the end users’ professional associations, then widely distribute.
“Possible” Definition

Recognition Criteria that includes clinical events that may occur as well as laboratory results/findings that may present for a recipient of a TISSUE allograft:

Clinical information that could be used as guidelines to qualify a “Possible allograft-transmitted infection” (this is not applicable to fresh skin allografts):

Bacterial/fungal:
  a. Signs of inflammation or infection (e.g., pain, swelling, purulent discharge, lymphadenopathy) from or near an operative site within 6 months of implantation associated with at least one of the following:
     1) fever
     2) positive culture or gram stain from within the operative site or from purulent drainage (not a superficial swab culture), or
     3) positive blood culture (consideration of other patient sources for the bacteremia must be investigated)

Parasitic/Viral:
  a. Signs and symptoms consistent with an unexpected viral agent or parasitic disease (e.g., fever, rash, lymphadenopathy, hepatitis), and/or
  b. Confirmed infectious disease test result (e.g., serologic, molecular) within one year post-implantation (compared to a negative infectious disease test result for the same test pre-implantation, if testing was performed)
Rationale for “Possible”

• Listings are manageable with reasonable sensitivity; do not desire reporting of common community-acquired diseases (colds, flu, etc.)

• Six-months selected (vs one year) as this is evidenced-based when investigating past tissue transmissions
Rationale for “Possible”

- Positive culture or gram stain from op site or from purulent drainage all describe relevant possibilities; superficial swab results have not correlated with allograft-transmitted infections
- TTSN system will have pulldown menu with these signs & symptoms and laboratory findings
Rationale for “Possible”

- Review of past reports in literature:
  - allograft removal has not been an indicator that would capture cases
  - Recognition of symptoms occurred between 2 to 113 days post op
  - Patient re-admission within 30-days of surgery
  - Cultured unexpected organisms from wound, drainage, or site
Proposed criteria follow describing information from investigation that could be used as guidelines to qualify a “Probable” allograft-transmitted infection.

**Bacterial/fungal:**
- A match between the culture findings in a recipient with the culture findings on pre-processing, in-process, or final cultures of any tissues from that donor, and/or
- Report of allograft-associated infection in other recipients of tissues from the same donor.

**Parasitic/Viral:**
- Confirmed infectious disease testing on an archived serum, plasma, or tissue sample from the implicated donor.
- Recipient diagnosed with a viral or parasitic infection with no known or identified risk factors for the disease.
- Report of allograft-associated infection in other recipients of tissues from the same donor.

To be considered a "Proven" allograft-transmitted infection, the following definition should be used.

Confirmation by appropriate laboratory testing (e.g., genotyping, PCR, wet prep) that demonstrates scientific evidence linking the infectious agent in the recipient with donor samples, or when testing is not possible, the presence of the same rare infection in both recipient and donor with no other identified risk in the recipient.
Indeterminate & Excluded

- Not yet developed....
Implant Card Compliance

2006 AATB Survey

“H1.410 Responsibility - The Tissue Bank shall establish recipient follow-up data collection protocols.”

- 15 tissue banks: \approx 95\% of all tissue processed in US
- 100\% offer feedback opportunity
  - Content of ‘cards’ fairly uniform
- Information rec’d is manually entered into a data base
- 53\% (8) routinely track compliance
  - Compliance range of 14\% to 95\%; \text{2/3 experience >50\% compliance rate}
2006 AATB Survey

“H1.410 Responsibility - The Tissue Bank shall establish recipient follow-up data collection protocols.”

• Most predominant information withheld = patient identifier, MR#

• End-user types most non-compliant
  ◆ Dental offices, oral surgeons
  ◆ Day surgery centers (independent)
  ◆ Large hospitals (university based)
Comments from Tissue Banks

- Difficulties with implant cards:
  - illegible handwriting
  - incomplete and/or inaccurate information

- No federal requirement. Why must we close this loop, especially when compliance is not controllable?

- Information supplied has limited, practical use
  - low return rate, data not sufficient for use during a recall or safety alert
Compliance is increasing due to:

- The Joint Commission’s Tissue Standards require it
- End user experience with large recalls
- Expectation is that tissue bank will track to recipient for them

Hospitals are beginning to use their own forms - this complicates the process
Thank you!

(questions will be entertained at the end)