Chapter 25

TOXIC EMBEDDED FRAGMENTS REGISTRY: LESSONS LEARNED

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INTRODUCTION

In 2008, the US Department of Veterans Affairs (VA) established the Toxic Embedded Fragment Surveillance Center (TEFSC; Baltimore, MD) in response to the growing number of service members who served in Iraq and Afghanistan and sustained an injury after contact with an improvised explosive device. At that time, it was estimated that 5,000 service members potentially had a retained embedded fragment as the result of such an injury.[1] As the conflicts continued, this number continued to grow, with one estimate reaching more than 40,000 service members (C. Perdue, personal e-mail communication, December 2009). In this context, the overall mission of the TEFSC is to

- identify veterans from these conflicts who may have retained fragments as a result of an injury they sustained while serving and
- conduct long-term medical surveillance of this population because of concern about potential local and systemic health effects related to the fragments.

Over the past several decades, there has been controversy about whether retained embedded fragments adversely impact health and warrant removal. In the past, retained embedded fragments were thought not to pose a significant health risk and, therefore, were often not surgically removed unless they caused the patient discomfort or were located in a joint space. For example, Machle[2] reviewed 40 bullet injury cases documented in the literature during the late 1800s and early 1900s. He reported that systemic lead absorption could occur from retained bullets, but that "lead poisoning" was a rare occurrence unless the fragment was located in a joint space.[2] It is important to recognize that, during this period, the ability to quantitatively measure lead exposure was limited. However, lead poisoning was defined then as having clinically overt symptoms related to exposure, including the presence of lead lines and visible central nervous system effects such as ataxia, memory loss, and convulsions. With significant improvements in exposure assessment methodology and a shift toward detecting preclinical disease, the definition of lead poisoning has changed dramatically. As a result, significantly lower lead concentrations have been associated with preclinical adverse health effects, thus raising the question about potential long-term health consequences related to systemic absorption of metal ions from lead fragments and, by inference, fragments of a different composition.

A more recent experience with embedded fragments of long residence time in the body was presented by the friendly fire incidents during the first Gulf War in 1991. During this war, depleted uranium (DU; a byproduct of the uranium enrichment process) was first used in the armor of tanks and in munitions used to destroy enemy tanks. Unlike lead, DU has radiological properties, as well as chemical properties, rendering it a dual health hazard.[3–5] During the 1991 Gulf War, a cohort of service members involved in friendly fire incidents was exposed to DU through inhalation, ingestion, and wound contamination when DU rounds were mistakenly fired upon their tanks.[6–11] Although there was the potential for adverse health effects related to short-term DU inhalation exposure and long-term DU exposure related to embedded fragments, service members involved in the friendly fire incidents were not immediately identified and followed as a cohort until the VA established a medical surveillance program in 1993.[6,7] Within this cohort of 80 individuals, urine measurements have consistently shown that service members and veterans with a retained DU fragment excrete higher concentrations of total uranium in their urine than those without fragments; these veterans have an isotopic DU signature (as opposed to a natural uranium signature), thus raising concern about target organ effects from systemic absorption of DU.[6–11] In addition, there is concern about local effects in areas surrounding fragments because research conducted in laboratory animals implanted with DU pellets has shown the formation of soft-tissue sarcomas in proximity to the implanted pellets.[11] Fortunately, more than 40 years of epidemiological evidence showing no increase in cancer rates in uranium fabrication workers[12] and more than 20 years of medical surveillance in the DU-exposed population have shown no clinically significant uranium-related adverse health effects.[13] Despite these findings, the initial delay in identifying those at risk for DU exposure led to criticism of the VA and raised concerns about whether critical windows of opportunity were missed to fully assess a veteran's exposure to DU early on.

Beyond the DU fragment example, other types of munitions have also raised concerns as potential long-residence, time-embedded fragments, including a recently introduced tungsten, nickel, and cobalt alloy. Although there have been no known friendly fire incidents resulting in embedded fragments of this type, Kalinich et al[14] found that laboratory animals implanted with pellets of this alloy excreted elevated concentrations of tungsten, nickel, and cobalt in their urine and developed rhabdomyosarcomas that quickly metastasized to the lung. This finding, combined with the experiences previously described, emphasized the need to better understand the types of exposures and potential human health effects that occur from materials embedded in the body. Thus, the VA established the TEFSC (at the Baltimore VA Medical Center) to address the following:

- limited information available regarding fragment composition related to improvised explosive device injuries,
- local and systemic adverse health effects resulting from embedded fragments, and
- delays in identifying and responding to potential hazards that could result in the loss of critically important, time-sensitive exposure information early after initial exposure.

In order to appropriately identify and conduct surveillance of veterans with embedded fragments, it is important to:

- anticipate the hazard and provide a timely response,
- recognize that exposure assessment is critical,
- obtain baseline biomonitoring data, and
- link surveillance data to clinical decision-making and medical management.

LESSON 1: ANTICIPATE THE HAZARD AND PROVIDE A TIMELY RESPONSE

Establishment of the Embedded Fragments Registry

To achieve its mission to identify affected veterans and to conduct medical surveillance of the population of veterans who have embedded fragments, the TEFSC established the Embedded Fragments Registry. In general, public health registries capture data in a systematic fashion to allow for population-level surveillance and identification of patterns and trends related to health status over time.[15] Historically, registries have been disease-focused, meaning data were collected on individuals who had a specific disease or health outcome of interest (ie, cancer). More recently, exposure registries that focus on the collection of data from populations with known exposures have also arisen.[16] Exposure registries are often established when specific health outcomes associated with an exposure are not well-characterized. Because long-term potential health outcomes associated with fragments are not well understood and the case definition for inclusion into the registry requires an indication that a veteran may have a fragment, the Embedded Fragments Registry is classified as an exposure registry.

Case Finding

As described by Gaitens et al,[17] the Veterans Health Administration developed a two-step screening process, which was fully implemented nationwide in 2009, to actively identify veterans who have embedded fragments and who receive care at a VA medical facility. Local VA healthcare providers are responsible for screening all veterans who served in Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn using a series of questions that are incorporated into the Computerized Patient Record System. These questions appear as "clinical event reminders" within the veterans' electronic health records and are automatically triggered based on the veterans' dates of service, thus alerting providers of the need to screen individual patients and allowing for more rapid identification of those at risk.

Screening Results

As shown in Figure 25-1, between November 2008 and June 2012 approximately one-half million veterans who served in Iraq and/or Afghanistan completed the *first phase* of the clinical reminder screening process, with 3.5% of these veterans indicating that they may have an embedded fragment as the result of an injury they received while serving in the area of conflict. The *second phase* of the screening process, which is also described in detail by Gaitens et al,[17] was initiated in October 2009 and contains questions regarding the cause of the injury (ie, bullet and/or blast or explosion), history of fragment removal and analysis, and identification of fragments that remain in the body. Responses to these questions trigger automatic inclusion in the Embedded Fragments Registry and are used to classify veterans into four exposure risk categories:

1. has/had a fragment,
2. has a high probability of having a fragment,
3. possibly has a fragment, or
4. likely does not have a fragment.

The automatic transfer of data into the Embedded Fragments Registry when the second phase of the screening process is complete alleviates reliance on providers to alert Center staff of individuals who are eligible for inclusion into the registry. As shown in Figure 25-1, almost 7,900 veterans potentially have a fragment and warrant further evaluation and follow-up. In addition to capturing responses to the screening questions for each veteran, the Embedded Fragments Registry captures other critical pieces of health and exposure-related information, such as fragment composition data and urine biomonitoring results from electronic medical record systems, as well as other available data sources.

Surveillance Protocol

Currently, the medical surveillance protocol—that includes fragment analyses, urine biomonitoring, and imaging of the fragment—is recommended for all veterans who may

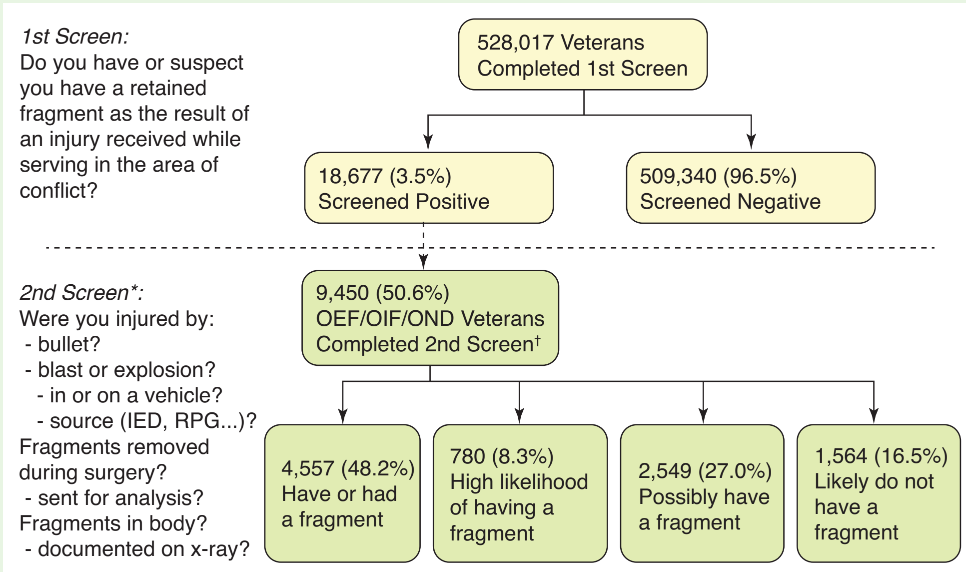

Figure 25-1. Screening results per June 30, 2012.
*Completion of the 2nd screen triggers inclusion in the Embedded Fragments Registry.
†486 of 9,450 (5%) veterans completed the 2nd screen, but had no indication of a positive 1st screen included in their electronic medical record.
IED: improvised explosive device; OEF: Operation Enduring Freedom; OIF: Operation Iraqi Freedom; OND: Operation New Dawn; RPG: rocket-propelled grenade

have a retained fragment. Analyses of the results from these activities, combined with other surveillance data captured in the Embedded Fragments Registry, will allow the VA to

- describe the population at risk for embedded fragments,
- characterize exposure related to retained fragments,
- consider potential health effects associated with specific fragment exposure, and
- utilize medical management guidelines to provide care for these veterans.

Fragment Analysis

In uncontrolled environments, such as war zones, it is often difficult to clearly identify and assess exposures at the individual level. In the case of embedded fragments, fragments that are removed during surgery or superficial fragments that work their way out of the body can be analyzed for composition to help characterize a veteran's exposure. Working with a specialized laboratory at the Joint Pathology Center (formerly located within the Armed Forces Institute of Pathology), the VA has established a process that permits VA providers to send such fragments for analyses to determine the composition of its inner and outer cores.[11] Working under the assumption that fragments remaining in the body are similar in composition to those that were removed, identification of the removed fragment materials provides crucial information needed to identify potential health outcomes of interest for an individual veteran and possibly to allow tailored surveillance for toxicants not typically included in a surveillance battery.

Understanding the importance of fragment composition data, in 2007, the Department of Defense (DoD) established a requirement for all military medical treatment facilities to send fragments removed during surgery to specified laboratories for content analyses in an effort to better characterize exposures and identify potentially hazardous embedded fragments.[18] The TEFSC reviewed aggregated fragment composition data from this effort to help develop their surveillance protocol and identify other methods for assessing fragment-related exposure when fragment composition data are not known for an individual service member. Knowing that the majority of fragments contain metals (eg, iron, lead, copper, aluminum, lead, and zinc) allowed the VA to develop a urine biomonitoring panel for toxicants of concern and to identify potential target organs at risk for adverse effects.[17]

The DoD and VA also established processes to allow for the transfer of fragment composition data at the individual level from the DoD to the VA's Embedded Fragments Registry. Currently, the registry is able to identify if a veteran has had a fragment removed and analyzed by the DoD and the results of the fragment analyses. This allows the medical surveillance protocol to be "tailored" to the individual and provides additional information that can be used for interpreting urine biomonitoring results.

LESSON 2: RECOGNIZE THAT EXPOSURE ASSESSMENT IS CRITICAL

Urine Biomonitoring

Urine biomonitoring offers several advantages for assessing fragment-related exposure. First, urine samples are noninvasive, posing no risk to the veteran submitting the sample. Second, monitoring the urine for concentrations of metals frequently found in fragments provides insight into exposure when specific fragment composition for an individual veteran is not known. Third, it helps determine the overall body burden of metals potentially related to fragments.

The TEFSC currently recommends that all veterans who may have an embedded fragment submit a 24-hour urine sample for analysis of concentrations of 14 metals; these metals have been found in fragments that have been removed during surgery from service members who served in the recent conflicts and/or are metals known for their toxicity.[17] All urine samples are submitted to the Baltimore VA Medical Center for creatinine analyses and to the Joint Pathology Center for measurement of the metal concentrations listed in Exhibit 25-1. The Embedded Fragments Registry electronically receives urine biomonitoring results—including creatinine concentrations, metal concentrations, and creatinine-adjusted concentrations—directly from the Baltimore VA Medical Center's laboratory system.[17]

Once results are obtained, creatinine-adjusted concentrations of the metals measured are compared with established reference values to gain insight into the composition of fragments that remain in the body.[11,17] For example, if a veteran's urine sample has a concentration of aluminum above what would be expected to occur in the general population and other sources of aluminum exposure have been ruled out, it is thought that the elevated aluminum concentration may be related to the composition of the fragment.

Over time, as fragments begin to oxidize in the body and changes to the fragments shape are detected on imaging, it is anticipated that higher concentrations of metals released from the fragments will be detected in the urine. Therefore, obtaining a "baseline' urine sample, as well as an X-ray film image of the area surrounding the fragment, as soon as possible after time of injury (or when the veteran transitions from active duty and presents to his/her local VA facility initially for care) are important factors in assessing long-term exposure risks. Although it can be difficult to obtain such data, because a veteran may not be currently experiencing health concerns and therefore not see the value in seeking care, waiting until a health concern presents may lead to more unanswered questions and difficulties in interpreting future urine biomonitoring results.

EXHIBIT 25-1

METALS INCLUDED IN THE URINE BIOMONITORING PANEL

Arsenic
Cadmium
Chromium
Cobalt
Copper
Iron
Lead
Manganese
Molybdenum
Nickel
Tungsten
Uranium
Zinc

LESSON 3: OBTAIN BASELINE BIOMONITORING DATA

Follow-up Actions Triggered by Urine Results

For all veterans who submit a urine sample or fragment for analysis, the TEFSC provides a letter of interpretation for the veteran and the veteran's VA care provider. Letters detailing urine biomonitoring result provide the creatinine-adjusted urine concentrations of each metal, as well as additional details about other potential sources of exposure, whether or not the levels found raise any health concerns, and describe how the urine results compare with fragment composition data, if available. Additionally, the provider letters contain specific recommendations for patient follow-up that include:

- imaging the fragment location with an X-ray film so that a baseline is obtained for future comparisons,
- assessing other potential sources of exposure (ie, occupation, hobby, dietary supplements),
- obtaining additional testing if necessary (ie, performing a blood lead test if urinary lead concentrations are elevated above the reference value), and
- describing a recommended timeframe for repeating urine biomonitoring.

The urgency of these actions depends on the magnitude of the excursion for a specific metal in relation to the reference value and how the result compares with levels linked to health effects in the literature.

The importance of a registry and continued follow-up may not be recognized by some individuals, clinicians included, because those individuals for whom data are collected often do not see the immediate benefits of such an endeavor. However, linking surveillance data to clinical decision-making and medical management provides the veteran and his/her healthcare provider with the information needed to anticipate potential health, possibly by taking preventive action or by detecting early health consequences of fragment-related injury.

LESSON 4: LINK SURVEILLANCE DATA TO CLINICAL DECISION-MAKING AND MEDICAL MANAGEMENT

Target Organ Surveillance

In addition to collecting the exposure data described previously, the Embedded Fragments Registry captures *International Classification of Diseases*, Ninth Revision, codes and clinical laboratory tests of interest directly from the patient's electronic medical record.[17] These measures were chosen by mapping the list of metals frequently found in fragments and including them in the biomonitoring panel to potential health effects and key target organs and systems (eg, the kidney, the immune system, and the reproductive system).[16] In the future, these health outcomes will be examined to detect patterns and trends in disease among those who have embedded fragments of known composition.

SUMMARY

Health concerns related to military deployment can be challenging to address, as potential hazards may not be immediately identified and individual exposures are often not well-characterized. Whenever possible, deployment-related hazards should be anticipated so that affected service members are easily identified and a response is implemented in a timely fashion. Assessing a service member's exposure to a hazard and obtaining baseline biomonitoring data can provide crucial information for determining the appropriate short- and long-term actions needed to mitigate potential health effects related to deployment. Based on these lessons learned from previous incidents, the VA established the Toxic Embedded Fragment Surveillance Center and the Embedded Fragments Registry to identify and conduct long-term medical surveillance of veterans who have embedded fragments. This exposure registry, which links surveillance data to clinical decision-making, will provide the VA with information needed to care for veterans with retained embedded fragments.

Acknowledgments

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