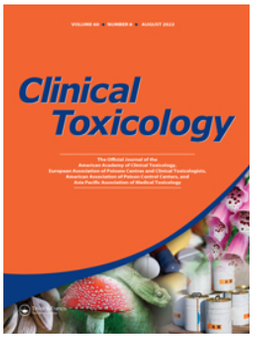

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# Retained bullets and lead toxicity: a systematic review

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REVIEW



# Retained bullets and lead toxicity: a systematic review

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**ABSTRACT**

**Introduction:** Lead toxicity secondary to retained bullet(s) (RB) after a penetrating gunshot wound is a rare but likely underdiagnosed condition, given the substantial number of firearm injuries in the United States. There is currently no consensus on the indications for surveillance, chelation, or surgical intervention.

**Objective:** The purpose of our review is to summarize the literature on systemic lead toxicity secondary to RBs to help guide clinicians in the management of these patients.

**Methodology:** The primary literature search was conducted in Medline (PubMed), EMBASE, Cochrane, and CENTRAL using the following MESH terms: "chelation" and "lead poisoning" or "lead toxicity" or "lead" and "bullet" or "missile" or "gunshot", or "bullet".

**Results:** The search identified 1,082 articles. After exclusions, a total of 142 articles were included in our final review, the majority of which were case reports. Several factors appear to increase the risk of developing lead toxicity including the location of the RB, the presence of a fracture or recent trauma, number of fragments, hypermetabolic states, and bullet retention duration. Particularly, RBs located within a body fluid compartment like an intra-articular space appear to be at a substantially higher risk of developing lead toxicity. Even though patients with lead toxicity from RBs will have similar symptoms to patients with lead toxicity from other sources, the diagnosis of lead poisoning may occur months or years after a gunshot wound. Symptomatic patients with high blood lead levels (BLLs) tended to improve with a combination of chelation and surgical removal of RBs.

**Conclusions:** We suggest surveillance with serial BLLs should be performed. Patients with intra-articular RBs appear to be at increased risk of lead toxicity and if possible, early surgical removal of the RBs is warranted, especially given that signs of toxicity are vague, and patients may not have access to follow-up. Long-term chelation should not be used as a surgical alternative and management should be multidisciplinary.

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**KEYWORDS**
Lead toxicity; retained bullets; retained lead; chelation; systematic review

## Introduction

There are an estimated 120,000 firearm injuries every year in the United States, the majority of which are nonfatal and occur in young males [1]. The prevalence of retained bullet(s) (RBs) from firearm injuries is unknown. Lead toxicity from RBs is likely underdiagnosed and under-reported given the substantial number of firearm-related injuries in the United States [1]. The challenge in identifying patients could be due to the vague symptoms of lead toxicity as well as the lack of surveillance for patients with RB. Currently, there is no consensus on the appropriate surveillance and management of these patients. Several questions still exist including the role for surveillance, chelation, and surgical indications, including prophylactic removal. From a toxicologic perspective, the best initial step to prevent lead toxicity is to remove the patient from the source of toxicity, which may be difficult and associated with surgical complications. However, new evidence and techniques have emerged for easier surgical removal in certain cases [2], including intra-articular RBs.

The purpose of our review is to summarize the literature on systemic lead toxicity secondary to RBs to help guide clinicians in the management of these patients. We aim to address the following: characteristics and location of RBs that increase the risk of developing lead toxicity; surveillance of blood lead levels (BLL)s; treatment of lead toxicity with chelation; and indications for surgical removal.

## Methods

### *Search strategy*

We conducted a literature search using the electronic databases: Medline (PubMed), Embase, Cochrane, and Cochrane Central Register of Controlled Trials (CENTRAL). We performed a search with the following MESH terms: "chelation" and "lead poisoning" or "lead toxicity" or "lead" and "bullet" or "missile" or "gunshot", or "bullet" for each database. We searched all of the above databases for the earliest publications they held until September 2021. We reviewed the bibliography listed in each of the articles for additional sources.

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We included all literature (including conference abstracts, case reports and case series) written in English regarding lead toxicity from RB that discussed either the epidemiology, risk factors, diagnosis, treatment, or surveillance. We included papers if they had a documented BLL but no signs of systemic lead toxicity. We excluded papers if they were duplicates, animal studies, had no history of a RB, oral ingestion of bullets or other etiologies for lead toxicity, or the absence of documented BLL and no symptoms of lead toxicity.

### Data abstraction

We distributed case reports and case series among ourselves to review. We were aware of the purpose of the review and had weekly meetings to discuss the data abstraction process. We entered data on a spreadsheet that, when present, included patient age, gender, location of bullet, time to onset of symptoms, reported symptoms, physical exam, hemoglobin nadir, presence of basophilic stippling, presence of lead arthrogram, initial BLL, peak BLL, treatments received (surgery, chelation, or both), timing of chelation in relation to surgery, duration of chelation, and post-treatment BLL. We categorized RB location into either "soft tissue", "joint", "spine", "bone with fracture", "eye/orbital/sinus", "body fluid compartment", or "multiple". We defined the location of "body fluid compartment" as a RB in contact with peritoneal, pleural, or cerebral spinal fluid. We defined "multiple" category as RBs located in at least two of the other categories unless the other category was soft tissue. If RBs were in soft tissue and one other category, we categorized the location into the other category. We assumed the typical dose and duration of each chelator if chelation duration was not specified. If only hematocrit was given, hemoglobin was calculated by dividing the hematocrit by three. We determined the presence of a lead arthrogram by a description of a lead arthrogram in the case report or a radiograph image with a visible lead arthrogram. We summarized the data as medians with interquartile ranges (IQR) or numbers with percentages using Excel (Microsoft, Redmond, WA).

## Results

Most of the literature on this topic consists of case reports and case series. The search identified a total of 1,082 articles (Figure 1). After exclusions, a total of 142 articles were included in our final review. There were 93 case reports, 13 case series, nine prospective trials, 13 retrospective cohorts, eight reviews, and six guidelines, conference abstracts, or letters to the editor. Among the case reports and case series, there were a total of 113 patients that we included in our analysis. All of these received a GRADE of very low quality of evidence because they were all patients exposed to an intervention and there were no controls. Demographics of the 113 case reports are summarized in Table 1. The median age was 34 years (IQR 21, 44) and 92 (81%) were male. The most common location was intra-articular, with the majority of these located in the hip and knee (Table 2). Patients with a RB in a body fluid compartment had the highest median BLL of 139 mcg/dL (IQR 53, 300) with a median time to symptom onset of 4 months. The majority underwent surgery and chelation. Overall symptomatic improvement was reported in 56 (50%). Four patients (4%) had no symptomatic improvement and 49 (43%) were either lost to follow-up or had no reported post-treatment course. There were a total of four deaths (4%). In the fatality cases, all developed severe encephalopathy and three developed seizures. While none of the fatalities were evaluated for other sources of lead, all had autopsies performed without another cause of death determined. One patient had only a urinary lead level, while the other three patients had a median BLL of 169 mcg/dL (IQR 167, 340) and median time to symptom onset of 7 months. Two of the deaths were associated with RBs in the knee and two had RBs located in a body fluid compartment. Body cavities contain mobile organs and extravascular fluid which augments the absorption of lead, leading to an increased BLL [3,4].

Details of patients with intra-articular RB are described in Table 3. The small number of patients with an elbow joint RB had the highest median BLL of 148.5 mcg/dL. Patients with a RB in the knee joint were the least likely to receive lead chelation. The median time until symptoms of lead toxicity was never less than one year and the overall median time until symptoms was 9 years.

The most common treatment included both lead chelation and surgery ($n = 54$, 48%) with symptom improvement in 37 (69%) patients (Table 4). Two (9%) of the patients who were not treated, and two (17%) only treated with lead chelation resulted in death. Patients who were treated with preoperative and postoperative lead chelation had the highest median BLL of 129 mcg/dL and 18 (72%) reported an improvement in symptoms.

### Factors that increase the risk for lead toxicity with retained bullets

We identified several features of RB potentially affecting risk of lead toxicity including location of the RB, presence of a fracture or recent trauma, number of fragments, hypermetabolic states, bullet retention time, and type of bullet.

#### Location

Overall, the risk of lead toxicity depends on the presence of an appropriate solvent and a rich vascular supply to the area where the bullet is lodged such as adipose and body fluids [5,6]. Several reports found that patients with bullets or fragments near a joint had a higher BLL than patients who did not [4,7,8]. The acidic nature of synovial fluid may double the solubility of lead in joint spaces compared to serum [6,9–11]. RBs in the joint are also subject to frictional forces which can lead to bullet fragmentation and dispersion of lead [12,13]. In our review, we found 46 patients with intra-articular RBs (Tables 2 and 3). Intra-articular RBs had a wide range of time until symptoms of lead toxicity developed (IQR 2.5, 20.8) with one patient requiring almost 21 years until symptoms presented. The majority of patients received

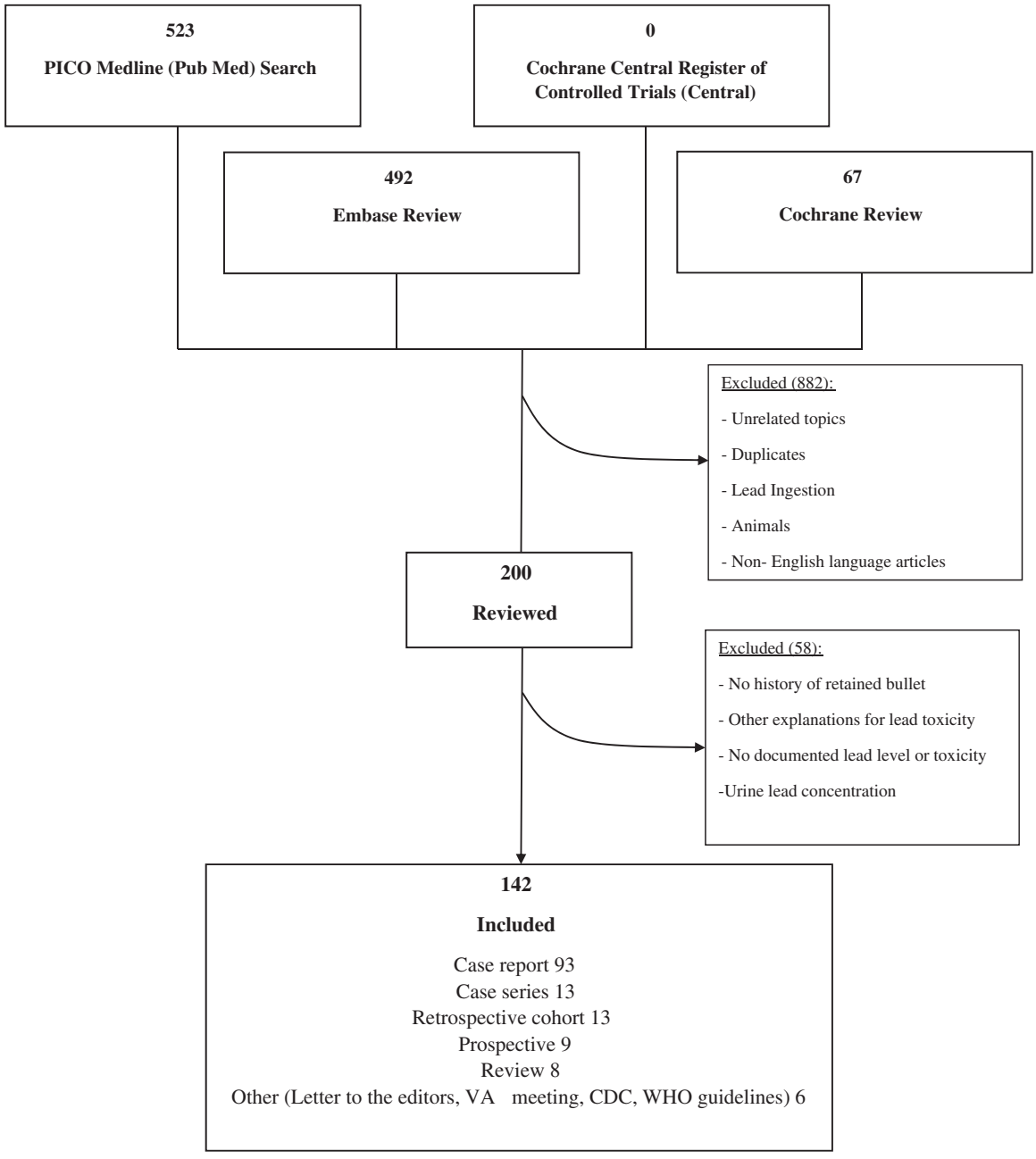


**Figure 1.** Flow diagram outlining study selection.

**Table 1.** Demographics of case reports.

| | |
|---|---|
| Total cases $n = 113$ | |
| Male *n*, (%) | 92 (81) |
| Median age in years, (IQR) | 34 (21, 44) |
| Lead toxicity symptoms reported *n*, (%) | 69 (61) |
| Median time to lead toxicity symptoms in years, (IQR) | 7 (0.5, 12) |
| Asymptomatic *n*, (%) | 29 (26) |
| Joint pain only *n*, (%) | 15 (13) |
| Blood lead level (BLL) reported *n*, (%) | 109 (96) |
| Median peak BLL in mcg/dL (IQR) | 84 (33, 144) |
| Median time post-exposure to peak BLL in years (IQR) | 5 (0.6, 12) |

surgical removal of RBs and were treated with chelation, and two patients with intra-articular RBs died.

In contrast, RBs found in soft tissue are often encapsulated and are traditionally thought to be less likely to result in lead intoxication [11]. Several patients did not develop lead toxicity despite having a RB in soft tissues [14–16]. The body surrounds lead fragments in fibrous tissue and may essentially remove the bullet from exposure to circulating body fluid and a vascular supply [10,17]. An exception to this protective effect would be the formation of a pseudocyst within the fibrous capsule. The fluid media within a pseudocyst, similar to other body fluids, can cause dissolution of the lead bullet, facilitating absorption [14,18]. This phenomenon is also observed with RBs near the spine where a bursa-like fluid collection can form [19]. We identified 10 patients of RBs in soft tissue (Table 2). Of these, 60% ($n = 6$) were lead intoxicated with a median onset of symptoms in seven years (IQR 0.5, 10). These numbers suggest that soft-tissue RB's may not be as benign as widely believed. However, several

Table 2. Characteristics based on RB location

| Location of RB | *n*, (% of total cases) | Lead toxicity symptoms reported *n*, (%) | Median time to lead toxicity symptom onset in years (IQR) | Median peak BLL in mcg/dL (IQR) | Received chelation *n*, (%) | Surgical debridement performed *n*, (%) | Improvement in symptoms *n*, (%) | Death *n*, (%) |
|---|---|---|---|---|---|---|---|---|
| Joints | 46 (41) | 27 (59) | 9 (2.5, 20.8) | 89 (58, 140) | 27 (59) | 35 (76) | 26 (57) | 2 (4) |
| Soft tissue | 10 (9) | 6 (60) | 7 (0.5, 10) | 84 (40, 215) | 5 (50) | 8 (80) | 4 (40) | 0 (0) |
| Eye/orbit/sinus | 13 (12) | 0 (0) | – | 14 (11, 19) | 1 (8) | 0 (0) | – | 0 (0) |
| Multiple locations | 13 (12) | 11 (85) | 8 (0.04, 12) | 129 (67, 157) | 12 (92) | 9 (69) | 9 (69) | 1 (8) |
| Body fluid compartment | 11 (10) | 9 (82) | 0.33 (0.16, 0.58) | 139 (53, 300) | 10 (91) | 8 (73) | 6 (55) | 1 (9) |
| Spine | 11 (10) | 11 (100) | 12 (7, 14) | 99 (73, 124) | 11 (100) | 10 (91) | 8 (73) | 0 (0) |
| Bones with fracture | 9 (8) | 5 (56) | 2 (1.8, 10) | 60 (44, 129) | 3 (33) | 8 (89) | 3 (33) | 0 (0) |
| Total | 113 | 69 (61) | 7 (0.5, 12) | 84 (33, 144) | 69 (61) | 78 (69) | 56 (50) | 4 (4) |

Table 3. Intra-articular RB case characteristics

| Joint Location of RB | Total *n*, (%) | Lead toxicity symptoms reported *n*, (%) | Median time to lead toxicity symptom onset in years (IQR) | Median peak BLL in mcg/dL (IQR) | Joint pain reported *n*, (%) | Anemia reported *n*, (%) | Lead arthrogram present *n*, (%) | Received surgery *n*, (%) | Received chelation *n*, (%) |
|---|---|---|---|---|---|---|---|---|---|
| Hip | 16 (36) | 14 (88) | 8.5 (1.3, 21.5) | 120 (35, 221) | 7 (44) | 11 (69) | 8(50) | 12 (75) | 8 (50) |
| Knee | 13 (29) | 6 (46) | 8.25 (1, 21) | 97 (62, 129) | 10 (76) | 7 (54) | 8 (62) | 9 (69) | 5 (38) |
| Foot/hand | 6 (13) | 2 (33) | 16 (14.0, 18.0) | 67 (62, 79) | 3 (50) | 2 (33) | 6 (100) | 6 (100) | 3 (50) |
| Shoulder | 4 (9) | 0 (0) | – | 94.5 (69, 99) | 3 (75) | 2 (50) | 3 (75) | 2 (50) | 3 (75) |
| Ankle/Wrist | 4 (9) | 3 (75) | 1.25 (1.3, 24) | 72 (53, 84) | 0 (0) | 2 (50) | 2 (50) | 4 (100) | 4 (100) |
| Elbow | 2 (4) | 2 (100) | 6,19 | 143,154 | 0 (0) | 2 (100) | 1 (50) | 1 (50) | 2 (100) |
| Total | 45 | 26 (58) | 9 (2.5, 20.8) | 89 (58, 140) | 22 (49) | 26 (58) | 28 (62) | 33 (73) | 24 (53) |

Table 4. Comparison of BLLs in different treatment groups.

| Treatment | *n*, (%) | Median pre-treatment peak BLL in mcg/dL (IQR) | Median post-treatment nadir BLL in mcg/dL (IQR) | Symptomatic improvement reported *n*, (%) | Death *n*, (%) |
|---|---|---|---|---|---|
| No treatment | 22 (19) | 12 (7, 18) | – | 2 (9) | 2 (9) |
| Chelation only | 12 (11) | 122 (68, 169) | 37 (32, 55) | 6 (50) | 2 (17) |
| Surgery only | 25 (22) | 54 (33, 79) | 45 (34, 51) | 11 (44) | 0 (0) |
| Both | 54 (48) | 128 (80, 180) | 34 (18, 48) | 37 (69) | 0 (0) |
| Total cases | 113 | 84 (33, 144) | 37 (20, 49) | 56 (50) | 4 (4) |

of these cases were complicated either by a concomitant fluid collection, recurrent trauma to the area, or patients with numerous lead pellets retained close to bone [17,20–22].

### Fractures

Patients with associated fractures have elevated BLL compared to patients with RB without fractures [7,23]. Fractures initiate a tissue inflammatory response which causes a release of lead from fragmented or healing bone [24,25]. New trauma at or near the site can result in an inflammatory response that can increase the release of lead from the RB. Several cases describe patients with prior RB that presented after new trauma with an elevated BLL [9,21,26].

### Metabolic state

Besides trauma, other hypermetabolic states appear to increase BLL from RB *via* inflammation, increased blood flow, or increased bone turnover. Physiologic stressors include infection, acidosis, altered bone metabolism, hyperthyroidism, and pregnancy [23,27]. Inflammation of the synovium favors passage of lead into the systemic circulation [12] *via* neovascularization [28]. These hypermetabolic states also increase the demands for calcium which may precipitate uptake of lead to be stored in the bone [23]. High BLLs may be seen in the first few months after injury when osteoclast activity is at its highest [7]. In one review of lead toxicity from RB, the majority had arthritis and chronic inflammatory changes at the fragment site [29].

### Bullet characteristics

Blood lead levels are influenced by the number of fragments and length of time they are in contact with bodily fluid. One review reported a single RB developed lead toxicity on average at 17 years, while shrapnel developed toxicity at 9 years, and buckshot on average of 8 months [29]. The higher number of bullet fragments or multiple pellets increases the surface area of lead in contact with tissues [8], increasing the likelihood lead will be absorbed [7,30]. Smaller fragment size may increase absorption as well [23]. Conflicting studies suggest the effect [5,9,11,13] or lack of effect [24,31] of exposure duration on BLL values.

Lead absorption from a RB also depends on the type of bullet present. Bullets are commonly composed of an outer jacket and inner core. The outer jacket can be made of

copper, nickel, steel, zinc, iron, or lead, while the inner core is usually lead-based. Lead toxicity can be influenced if the bullet is jacketed or unjacketed [32]. Bullets not fully jacketed will deform or fragment when impacting bone and potentially expose a larger surface area of lead to tissues [23]. Higher tissue levels of lead and zinc were found in gunshot wounds with unjacketed bullets compared to jacketed bullets [32].

## Clinical presentation of lead toxicity from retained foreign bullets

Patients with lead toxicity from RBs will present similarly to patients with lead toxicity from other sources. However, there are multiple challenges in the diagnosis of lead toxicity from RBs. The presentation of lead intoxication can be insidious and symptoms are nonspecific, often not identified until severe toxicity is present [23]. It can also be difficult to connect RBs to a patient's symptoms, especially when the gunshot wound occurred years prior. The major organ systems involved in lead toxicity include neurologic, gastrointestinal, renal, cardiovascular, hematologic, and musculoskeletal. It is important for clinicians to be aware of the risk of lead toxicity in cases of RBs and consider it in the setting of weight loss, gastrointestinal complaints, neurologic findings, and anemia.

Many patients with RBs presented multiple times to healthcare facilities before the final diagnosis of lead toxicity was elucidated [12,33]. Case reports describe five emergency department visits for recurrent symptoms such as abdominal pain [21,34]. Another case reported greater than 10 admissions before the diagnosis was discovered [35]. In some cases, the diagnosis of lead toxicity from a RB was not made until autopsy [6,18]. Lead toxic patients often present with weight loss, weakness, fatigue, or loss of appetite [5,18,21,31,36–41]. These cases demonstrate that nonspecific complaints of lead toxicity are more likely to be attributed to more common medical conditions leading to delays in diagnosis and treatment.

### Neurotoxicity

As with lead poisoning from other routes of exposure, neurologic effects are the most concerning and consequential. Many patients with lead toxicity from RB presented with headache, tremor, numbness and paresthesias [9,31,33,41–43]. In some cases, patients develop nerve palsies, hyper- and hyporeflexia, and sensory deficits [5,10,44,45]. Some patients progressed to encephalopathy, and seizure [14,18,35,46–48]. In addition, irritability, hallucinations, and memory impairment have also been reported [49–51].

### Gastrointestinal toxicity

Gastrointestinal effects are commonly seen in all types of lead poisoning but are nonspecific. The majority of patients present with at least one gastrointestinal symptom, including abdominal pain with nausea, vomiting, and constipation [5,14,29,31,33,36,37,39,49,52–54].

### Musculoskeletal

Many patients also reported musculoskeletal pain including arthralgias, myalgias, and muscle wasting [5,10,14,29,31,37,48,55]. Besides lead toxicity contributing to musculoskeletal symptoms, residual musculoskeletal dysfunction from the bullet injury may have contributed to pain.

## Physical examination and laboratory findings of lead poisoning

There are laboratory and clinical exam findings that can help direct clinicians to the diagnosis of lead toxicity from RB. Lead inhibits multiple enzymes in the heme synthesis pathway, leading to anemia [10,14,35,47,56–58]. In our analysis of the 113 cases, the median hemoglobin nadir was 9 g/dL (IQR 7, 11). Basophilic stippling occurs by inhibition of pyrimidine-5′-nucleotidase results in clumping of degraded RNA [5,14,18,21,29,36,38,40,49,54,59,60]. Out of the cases we analyzed, 32 (28%) reported basophilic stippling. Gingival or Burton's lead lines are another exam finding that may be present [5,10,18,21,29,44,49,54].

## Management

### Initial surgical removal

Management of patients with RBs can pose many challenges to clinicians. There is no reliable evidence to help clinicians determine which patients require surveillance or treatment. Recently, the Center for Disease Control (CDC) lowered the BLL threshold for pediatric patients from 5 mcg/dL to 3.5 mcg/dL for evaluation of possible sources of exposure and primary prevention [61]. The World Health Organization (WHO) recommends clinical evaluation and termination of the source of lead for anyone with a BLL of 5 mcg/dL or greater [62]. In the case of RBs, primary prevention of lead toxicity requires removal. The longer the RB is allowed to remain in place, the more lead is absorbed and stored in bone [18,29,33]. Some authors have argued that leaving RBs in place may make later surgeries more difficult as the metal dissolves [63], while some have advocated for early surgical removal of RBs in certain cases [7,18]. From a surgical perspective, there is no reliable evidence in support of routine RB removal. Surgical removal can be associated with risks and complications or may not be feasible given the anatomic location and degree of fragmentation (Figure 2). One study found that of 202 patients discharged with an RB, only four required later removal [64]. Prior authors have suggested that surgeons should be selective in which RBs they remove and that intra-articular, location within a vessel lumen, or nerve impingement are clear indications for RB removal [65–67]. Arthroscopic removal of intra-articular RBs has successfully been performed and may be a less invasive alternative to open techniques in the appropriate clinical setting [68–72].

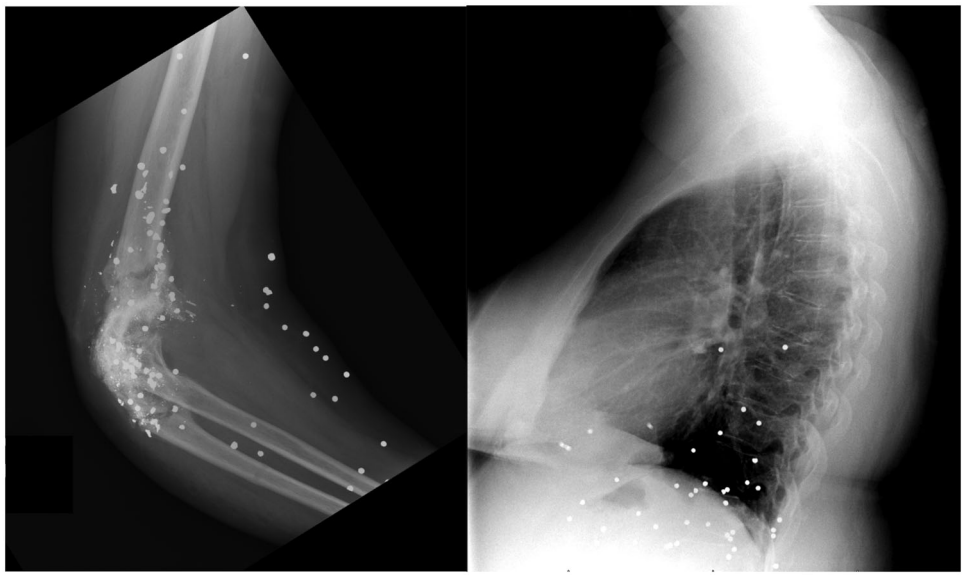

Figure 2. Radiographs of an elbow and chest demonstrating multiple pellets and difficulty with surgical removal because of anatomical location and fragmentation. Consent to publish this image was obtained directly from the patient.

For the majority of RBs located in soft tissue, initial surgical removal is not routinely recommended [71,72]. While initial removal of soft tissue RBs may not be warranted, clinicians should be aware that these patients can develop lead toxicity and should provide BLL surveillance. In contrast, initial removal of intra-articular RBs has long been recommended due to the increased risk of lead toxicity and joint destruction [13,29,70,72,73].

Due to the risks associated with removal of intra-orbital RBs and the low occurrence of lead toxicity in these patients, surgical removal should not be routinely attempted [74]. We identified 13 cases of RBs in the orbits or sinus (Table 2). None were symptomatic for lead toxicity and the median peak BLL was 14 mcg/dL (IQR 11, 19 mcg/dL). One case summarized a 4-year-old boy with RBs in the right orbit and paranasal sinuses who had a BLL of 42 mcg/dL but was asymptomatic [75]. In this case, the risks of surgical removal were thought to outweigh the risk of chronic lead exposure. He received multiple rounds of chelation with rebounding BLLs and was eventually lost to follow-up. The authors discuss weighing the risks and benefits of long-term chelation in these patients with continuing lead exposure.

Recently, some studies have recommended nonoperative management of certain abdominal penetrating traumas [76,77] which may increase the number of patients with intra-abdominal RBs in contact with intraperitoneal body fluid. Our review identified 11 cases with RBs located in a "body fluid compartment" like pleural or peritoneal fluid. Nine (82%) had symptoms of lead toxicity within a median of 0.33 years (IQR 0.16, 0.58) and a median BLL of 139 mcg/dL (IQR 53, 300). Patients not suitable for operative management, should undergo monitoring for the development of lead toxicity [78].

Our review identified only 11 published cases of lead toxicity from RBs in the spine. All patients had lead toxicity symptoms. Two of these patients had associated pseudocysts [5,18]. Given the high rates of complications from surgical removal of RBs in the spine, one author recommended that removal should not be done solely for prevention of lead toxicity but may be warranted if BLLs rise with annual monitoring [19].

Prior studies have suggested that low-velocity gunshot wounds associated with fracture can be treated nonoperatively while high-velocity or grossly contaminated injuries should be operatively washed out and debrided [71,79]. We reviewed nine patients with RBs in bones associated with fractures (Table 2). Five of these patients had fractures of the femur and three had fractures of facial bones.

While there are patients for whom surgical removal may not be feasible or may pose greater risk to the patient, long-term medical management with chelation is also not reasonable given the cost, side effects, and periodic national shortages of chelators [78,80]. For these patients, an interdisciplinary management plan could help to achieve the best patient-centered care. Factors such as patient comfort, age, medical comorbidities, ability to have adequate follow-up, desired future fertility, chelator availability, and costs can be discussed between the specialties to determine the best approach on a patient-by-patient basis.

## *Surveillance of patients with RBs*

***Blood lead level (BLL) monitoring.*** There are no reliable data to provide evidence-based guidelines regarding appropriate monitoring of BLLs. In one series, patients with RBs had higher mean BLLs than patients without RBs (17 mcg/dL in RB group versus 7 mcg/dL) [81]. Another series of 451 patients with extra-articular RBs found that 2.1% of patients had a BLL $>$ 10 mcg/dL on the day of injury which increased to 38.1% of patients by 3 months post-injury and then decreased by 12 months (20.8%) [7]. In contrast, patients with RBs in facial soft tissue did experience an increase in

Table 5. Recommended MANAGEMENT OF PATIENTS with Retained Bullet (s) (RB)s.

**General**
- Educate patients on the signs and symptoms of lead toxicity
- Counsel female patients on increased risk of infertility, lead toxicity to fetus, and need for early intervention
- Chronic chelation is not an alternative to surgical removal but may be used as an adjunctive therapy

**All patients at time of initial injury obtain:**
- Baseline blood pressure
- Venous BLL, ZPP, CBC, creatinine, UA
- Radiographs of RBs

**Asymptomatic patients:**

**If surgical removal is not immediately feasible**
- Obtain venous BLL
  Adults: Monthly for first 3 months followed by annually[7,24,46]
  Children: Follow CDC testing recommendations[4]
- If venous BLLs are rising
  - Consultation with a surgical service for removal
  - Obtain repeat ZPP, CBC, LFTs, creatinine, UA, assessment for HTN
  - Evaluate for other possible sources of lead
  - Consult toxicology for evaluation and possible chelation therapy if BLL is
  - $\geq$ 70 mcg/dL for adults
  - $\geq$ 45 mcg/dL for children[a]
- Obtain radiographs of RBs as clinically indicated

**Symptomatic patients**
- Evaluate for other possible sources of lead
- Consult surgical service for urgent removal of RB
- Consult toxicology or poison control center for consideration of chelation therapy
- Obtain BLL, CBC, creatinine, ZPP, LFTs, UA
- Obtain radiographs of RBs and/or CT imaging for surgical planning

[a]Although CDC and WHO guidelines do not recommend routine chelation for pediatric patients at 20-44 mcg/dL, some clinicians may opt to chelate at this BLL.

BLL: blood lead level; ZPP: zinc protoporphyrin; CBC: complete blood count; UA: urinalysis; LFT: liver function tests; HTN: hypertension; CDC: Centers for Disease Control and Prevention; WHO: World Health Organization; CT: computed tomography

BLL post-injury, but the mean level was still below CDC threshold for intervention [30]. Similar to this study, the mean BLL in patients with RB was 6.7 mcg/dL compared to 3.2 mcg/dL in the control group and that the slight increase in BLL did not change management [24]. Some recommendations on monitoring BLLs have been published, though often were based on a small number of patients. One author suggested routine monitoring as long as lead is in contact with body fluids [38]. One case series of 15 patients with RB for $>$ 40 days suggested there was no need to measure levels one year after injury unless patients became symptomatic [82]. Several authors suggest obtaining BLLs every two weeks after injury followed by monthly until three months post-injury then annually [7,25,46]. A multidisciplinary workshop at Veterans Affairs Walter-Reed Hospital recommended an annual BLL in patients with RBs [83].

Our review demonstrated that patients with RBs can become lead intoxicated several years to decades after their initial injury. Of 113 patients analyzed in our review, the median time to lead toxicity was seven years (IQR 0.5, 12) with the longest delay of 52 years. We recommend a surveillance schedule as outlined in Table 5. As previously described, this is based on a low level of evidence. Exercising clinical judgment and consultation with a toxicologist or poison control center can offer guidance on a patient-by-patient basis.

We suggest that patients with RBs in soft tissue should have annual surveillance of BLLs and be counseled on the symptoms of lead toxicity [83]. Clinicians should obtain a BLL if signs or symptoms concerning for lead toxicity develop. We recommend that patients with an intra-articular RB in close proximity to a bone, joint, or area of body fluid compartment (pleural, peritoneal, bursa, cerebrospinal fluid) have a baseline BLL obtained at the time of injury, followed by a level monthly for the first three months, then annually [7]. Given the increased morbidity and long-term effects of lead toxicity on pediatric patients, we recommend the surveillance guideline as outlined by the CDC [84].

***Other laboratory studies.*** While some clinicians obtain a screening capillary blood test for lead, it requires confirmation with a venous BLL [84]. Since many RB patients are likely to have elevated BLLs compared to the general population, we recommend obtaining venous BLLs rather than capillary to avoid a delay in diagnosis [7,24,30,81].

Obtaining a zinc protoporphyrin (ZPP) level at the time of initial injury can assist with determining baseline chronic lead exposure. ZPP elevation lags behind elevated BLL by 8 to 12 weeks and will not be elevated in an acute lead exposure [85]. Repeating a ZPP level when BLL is rising or when a patient becomes symptomatic may be useful in determining other recent lead exposures. If the ZPP is low, it may be indicative of an alternative new source of lead other than the RB. Free erythrocyte protoporphyrin (FEP) level is a similar marker for chronic lead exposure but has largely been replaced by ZPP.

If venous BLL is rising, a complete blood count (CBC) should be monitored for evidence of normocytic or microcytic anemia and basophilic stippling. If chelation is being considered, liver function tests, and a basic metabolic panel should also be obtained.

***Imaging.*** Radiographs can be useful in determining total body lead burden by evaluating the location and number of bullet fragments as well as possible migration over time [83]. If the RBs are intra-articular, radiographs may demonstrate the formation of a "lead arthrogram" in which the lead bullet has partially dissolved in the synovium and the metal coats the joint cavity, indicating an increased risk of lead toxicity [38]. One case described the temporal course of joint destruction and dissolving RB over 28 months with eventual disappearance of the lead arthrogram, indicating likely systemic absorption of lead [86]. In our review, 62% ($n = 28$) of the RBs located in joints demonstrated a lead arthrogram or bursogram over time (Table 3). Surveillance radiographs can also demonstrate joint destruction and the development of arthritis, which may prompt surgical intervention. For these reasons, we recommend periodic radiographs as clinically indicated if the RB is near a joint to monitor for developing complications.

Computed tomography (CT) may be helpful for surgical planning. However, images may be difficult to interpret due to artifacts from the RBs. We recommend against routine surveillance CTs. MRI is contraindicated in the setting of retained metal. Ultrasound is increasingly available in many healthcare settings and may be useful in detection, surveillance, and removal of an RB. There are reports of ultrasound

being used for removal of a RB [87] and exploration of a RB in the neck [88].

### Delayed surgical management

If lead toxicity develops or BLLs rise, surgical removal should be considered to prevent continued systemic absorption of lead. Our review demonstrated multiple cases in which lead toxicity symptoms improved or BLL significantly dropped after surgery [2,5,8–10,17,18,20–22,25,29,33–36,38,40–46,48,49,53,54,57–60,89–100]. Of the 79 patients who received surgery, with or without chelation, 61% ($n = 48$) had improvement in symptoms. There were no deaths in this group. The 34 patients who did not receive surgery, with or without chelation, 12% ($n = 4$) died and only 23% ($n = 8$) had an improvement in symptoms. These cases suggest surgical removal of RB is critical to prevent ongoing degradation of the bullet and further systemic absorption of lead. However, due to the storage of lead in bone overtime, delayed surgical removal of RBs is unlikely to result in complete removal of lead and continued surveillance is necessary.

### Chelation treatment

In our review, 12 patients with RBs treated with chelation only, had a drop in BLL from a pre-treatment median of 121.5 mcg/dL (IQR 68, 169) to post-treatment BLL 37 mcg/dL (IQR 32, 55) and 50% ($n = 6$) had symptomatic improvement. However, there were 2 deaths (17%) in the chelation only group. Several reports demonstrated a failure of multiple courses of chelation to adequately lower BLL and patients ultimately required surgical removal [5,17,48,52,91,94]. Notably, one patient had over 10 admissions for lead toxicity (BLL > 100 mcg/dL) and received multiple courses of chelation until surgical removal was performed [35]. Chelation therapy only minimally reduces total body lead burden by 1-2% [101,102] and has not been proven to have long-term clinical benefits [103,104]. Even if a course of chelation significantly reduces the BLL, the effect is likely temporary as lead from the RB continues to be released from bone and the remaining RB. WHO guidelines state there is limited value of chelation therapy with ongoing lead exposure in adults. Protracted chelation may be reasonable in selected pediatric patients with severe poisoning as a life-saving measure when surgical removal is not feasible [62]. Because of these factors and the expense, side effects, and chelation shortages, we recommend against a chelation-only treatment plan.

***Pre-operative chelation.*** Some authors have previously argued that surgery without prior chelation could be dangerous due to theoretical mobilization of lead to the systemic circulation during surgical manipulation [9,18,38]. In our review, no patients who received surgery without prior lead chelation had worsening signs of lead toxicity in the postoperative period. However, the median preoperative BLL of those who did not receive preoperative chelation was lower than those who did (45 mcg/dL versus 103 mcg/dL). Based on limited evidence, we think it is reasonable to pre-operatively chelate lead for patients who are symptomatic for lead toxicity or adult patients with levels ≥ 70 mcg/dL and pediatric patients with levels ≥ 45 mcg/dL. There was not sufficient evidence to suggest a BLL goal prior to surgery. Linden *et al* suggested a goal BLL of < 80 mcg/dL [18]. There is also little evidence to guide clinicians on the most appropriate chelating agent and this was beyond the scope of this review. Generally, adult patients with mild symptoms or BLL between 70-100 mcg/dL can be treated with the standard course of succimer (10 mg/kg three times daily for five days followed by 10 mg/kg twice daily for 14 days), while more symptomatic patients or those with BLL > 100 mcg/dL are treated with calcium sodium EDTA and dimercaprol (BAL). There are several reports in the literature of symptomatic patients successfully treated with succimer alone or succimer and dimercaprol preoperatively [3,38,41].

***Post-operative chelation.*** Since over 90% of systemically absorbed lead is incorporated into bone over a period of several months, it is reasonable to assume that patients with RBs for prolonged periods will likely continue to redistribute lead and have elevated BLLs even after the lead source has been removed [29,33,41,105]. In our review, there were only five patients treated with only postoperative chelation. The median preoperative BLL of these patients was lower at 35 mcg/dL (IQR 30, 148) than other groups and only two patients had symptomatic improvement. Compared to that group, those who received lead chelation preoperatively and postoperatively ($n = 25$) had a median BLL of 129 mcg/dL (IQR 100, 228), postoperative median BLL of 30 mcg/dL (IQR 20, 47), and 72% ($n = 18$) had symptomatic improvement. The majority of patients received postoperative lead chelation with oral agents like succimer or D-penicillamine. WHO guidelines state that BLLs should be monitored 2 to 4 weeks post-treatment, but risks and benefits should be assessed for ongoing chelation therapy. Additionally, WHO advises that if four to five chelation cycles have been performed and the BLL continues to be ≥ 45 mcg/dL without improvement from baseline BLL, the patient should be evaluated for an alternative source of lead [62]. Some patients in our review received multiple courses of postoperative lead chelation due to elevated BLLs. One case described a patient in which 10 standard courses of succimer were administered for chronically elevated BLL (50-70 mcg/dL) despite symptomatic improvement [99]. Another case described chronically elevated BLLs despite multiple courses of succimer [41]. In this case, the cost of succimer was a barrier to continuing therapy and instead treatment was targeted to symptom management rather than BLLs.

It is reasonable to offer postoperative lead chelation for symptomatic patients, adult patients with BLLs ≥ 70 mcg/dL, and children ≥ 45 mcg/dL. Repeat BLLs should be obtained 2 to 4 weeks after chelation therapy [62]. After this, chelation therapy should be targeted to symptom mitigation and biochemical evidence of toxicity (anemia, basophilic stippling) rather than BLL.

## Limitations

Our review has several limitations. The majority of publications on RBs and lead toxicity consist of low-quality evidence

such as case reports and case series. Any conclusions or recommendations based on these cases are at risk for bias. RB cases with obvious lead toxicity would appear more often in publications than RB cases without lead toxicity. Cases that received surgical intervention are also more likely to be published compared to cases that did not receive surgical intervention. Therefore, our review has publication bias, and we cannot adequately compare the patients with RBs who developed lead toxicity to the patients with RBs who did not develop lead toxicity. Our review is also at risk of information and selection bias given that not all publications discussed ruling out alternative sources of lead toxicity and many were lost to long-term follow up. Given these limitations, we recommend that clinicians caring for patients with RBs discuss management with a toxicologist on a case-by-case basis.

## Conclusions

Retained bullets (RBs) uncommonly cause lead poisoning, although it is likely an underdiagnosed condition given the substantial number of firearm injuries in the United States. With no clinical trials to inform our management of RBs, we rely heavily upon case reports and case series. The diagnosis of lead toxicity may be missed due to the vague signs and symptoms, delayed onset, and lack of adequate follow-up in this patient population. Overall, our review suggests that patients with intra-articular RBs are at increased risk of lead toxicity. Long-term chelation should not be used as an alternative to surgical intervention given the continued exposure to lead, cost of chelation, chelation shortage, and side effects. We recommend multidisciplinary management that includes a coordinated effort among the surgeon providing RB removal, primary care physician for continued surveillance, and the clinical toxicologist's assessment of lead toxicity and the need for chelation.

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