REVIEW

Aluminum contamination in parenteral products

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Purpose of review
In 1986, the US Food and Drug Administration issued an aluminum mandate in hopes of minimizing patient exposure to aluminum contaminates contained in parenteral nutrition additives. The purpose of this article is to revisit the status of aluminum contamination as it relates to parenteral nutrition and to survey the recent literature to determine if any new findings have emerged. A special emphasis will be placed on the complications associated with aluminum toxicity.

Recent findings
In addition to metabolic bone disease, patients with aluminum toxicity are also prone to other complications such as neurodevelopmental delays and cholestasis. Other potentially serious consequences, including osteoporosis, growth failure, and dementia, can arise years after the initial exposure to aluminum, showing that preventing toxicity is imperative.

Summary
Unlike the rapid response to eliminating aluminum toxicity in the dialysis patient population, similar successes have not been realized in patients receiving parenteral nutrition solutions. Product formulation changes have been slow to emerge from manufacturers. It remains the responsibility of healthcare practitioners to recognize the patient populations at risk for toxicity and act accordingly. Monitoring aluminum status and purchasing products known to possess the least amount of aluminum are two such approaches.

Keywords
aluminum, metabolic bone disease, parenteral nutrition

INTRODUCTION

The 1986 US Food and Drug Administration (FDA) aluminum mandate was issued to minimize patient exposure to aluminum in parenteral nutrition additives [1▪]. In 2000, probably in response to the sheer difficulty in manufacturing aluminum-free parenterals in a cost-effective manner, the mandate was modified such that the FDA simply required that the aluminum concentration be noted on the labels of all additives used to compound parenteral nutrition. Large-volume parenterals (that is, sterile water for injection, amino acids, dextrose) had established limits on the maximum aluminum concentration (25 μg/l), but small-volume parenterals were simply required to label their products with the maximum aluminum content at the time of the expiry. Pharmacists were expected to use these values to calculate the maximal amount of aluminum contained in a patient's parenteral nutrition formula and inform the prescriber of the potential for aluminum loading and toxicity. As these calculations are based on the aluminum content on product label when the product expires and not the actual amount contained at the time of compounding, the potential for overestimation exists. As a result, many practitioners opted to monitor their patient's serum aluminum concentrations, rather than to make clinical decisions based on a theoretical risk [1▪]. The purpose of this article is to revisit the status of aluminum contamination as it relates to parenteral nutrition and describe the potential complications associated with excessive aluminum intake.

BACKGROUND

The third most abundant mineral within the earth's crust, aluminum is found in almost every plant and animal tissue [1▪]. Most adults ingest between 3 and 5 mg aluminum on a daily basis [2▪]. The first cases of aluminum toxicity were reported in the 1970s

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KEY POINTS

- Little progress has been made in reducing the amount of aluminum contamination present in additives used to compound parenteral nutrition solutions.
- In addition to metabolic bone disease, other complications associated with aluminum toxicity include growth delays, parenteral nutrition associated cholestasis, and anemia.
- Many complications associated with excessive aluminum intake do not manifest until years after exposure.
- Infants and children appear to be particularly susceptible to aluminum toxicity-related complications.

when reports of osteomalacia and encephalopathy secondary to aluminum exposure were observed in dialysis patients [1▪]. Similar symptoms began to appear in the 1980s when parenteral nutrition use became more prevalent. Cases of encephalopathy and osteopenia were linked to parenteral nutrition aluminum contaminates [1▪]. Although the renal community was able to minimize exposure by changing how water used in dialysis baths was prepared, similar changes in manufacturing methods have not occurred with parenteral nutrition additives.

ALUMINUM PHARMACOKINETICS

The systemic absorption of aluminum is minimized by numerous natural protective barriers. Healthy adults absorb 0.3–0.5% of the 5 mg/day aluminum present in a typical oral diet [1▪]. Although aluminum absorption can occur at low or neutral pH, like most medications, little occurs in the stomach. In the alkaline environment of the small intestine, aluminum is converted to insoluble salts and is not available for uptake. Aluminum may be absorbed in the small intestine if it has previously been complexed with organic molecules in the stomach, allowing it to remain soluble in the higher pH environment. [2▪] In fact, large intakes of citric acid, such as in orange and lemon juice, can enhance enteral aluminum absorption by forming nonionized aluminum citrate that can pass through the gastrointestinal barrier. The aluminum that does get absorbed and reaches the systemic circulation becomes protein bound and renally excreted with small amounts cleared in the bile [1▪]. More than 95% of aluminum is renally excreted, following a biphasic pattern [2▪]. Initially, during the first hours after intravenous administration, levels are low but gradually rise and peak within 24–48 h. In instances of excessive intake, the limits of total fecal excretion are exceeded and additional aluminum can be absorbed and reach the systemic circulation. Intravenous administration of aluminum-contaminated products bypasses the protective barrier of the gastrointestinal tract and accumulates in bone, liver, kidney, brain, and other tissues. The amount of aluminum that can be deposited varies with age. In neonates, approximately 75% of parenterally infused aluminum is retained, in comparison to 40% in adults [2▪]. Moreover, once deposited in the body, aluminum can remain in tissues for years with a half-life as long as 7 years [1▪].

DIAGNOSING ALUMINUM TOXICITY

There is no standardized test to make a diagnosis of aluminum toxicity. It is often made after obtaining a thorough medical history and evaluating clinical signs and symptoms along with imaging and laboratory studies. Nonspecific symptoms such as mental status changes, bone pain, and multiple nonhealing fractures may be present [1▪,2▪]. In patients with renal disease, plasma aluminum levels have long been used as a predictor of metabolic bone disease. Likewise, blood levels continue to be a poor predictor of presence or absence of toxicity. Reference ranges are used as guidelines to identify populations at risk for toxicity but may not reflect exposure or the potential to cause adverse effects. Because aluminum is ubiquitous, obtaining and analyzing samples with minimal contamination remains a challenge. Moreover, circadian rhythm changes in aluminum levels (that is, higher in the morning and lowest in the early evening) make timing of sample collection an additional consideration. A recent study showed that there was a wide variation in reference aluminum ranges even if the same analytical method was used [3▪]. Urine concentrations have also been used, but the relationship of these levels to disease severity has not been clearly demonstrated [1▪]. Likewise, assessment of hair aluminum content is not considered a standard (or optimal) test for monitoring aluminum status [2▪]. The deferoxamine infusion test has been used to determine aluminum load [1▪]. Deferoxamine, a chelating agent, removes aluminum from tissue stores and allows for more accurate assessment of serum aluminum levels. As part of this diagnostic test, baseline aluminum levels are obtained, an infusion of deferoxamine is administered, followed by a repeat serum aluminum level. Toxicity is present if the serum aluminum rises after the deferoxamine infusion. Although this test has been used to determine aluminum toxicity in dialysis

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patients, there is no standard protocol to guide practitioners in the assessment aluminum toxicity secondary to parenteral nutrition exposure [1▪]. Because of the difficulties in recognizing toxicity and accurately measuring aluminum levels, the actual prevalence of aluminum toxicity in the parenteral nutrition dependent patient still remains unknown. Other complications that appear years later, such as osteoporosis, may offer some insight.

MANAGEMENT STRATEGIES

Treatment options in the management of aluminum toxicity remain limited. Deferoxamine chelation therapy has been used to treat parenteral nutrition associated aluminum toxicity [4▪]. This therapy, however, has its own risks, including hypocalcemia [1▪,5]. Prevention of toxicity by reducing or eliminating aluminum-rich additives continues to be the most effective means of management.

Other measures that can potentially minimize the complications associated with aluminum toxicity include the provision of the amino acid taurine and correcting any underlying iron deficiency. Taurine mitigates aluminum toxicity by improving the cellular antioxidant defense system by stabilizing the cell membrane, thus preventing lipid peroxidation. It may also help decrease aluminum-associated hepatoxicity, given its similar chemical activity as acetylcysteine and its precursor cysteine that has been shown to have some efficacy as an antioxidant [6]. More recent evidence suggests that pretreatment with taurine confers the similar protection against aluminum-induced nephrotoxicity [7▪].

Supplementing with iron can also reduce aluminum toxicity by binding to transferrin, the primary aluminum-binding ligand. By preventing iron deficiency, the affinity of transferrin to aluminum is reduced and less free aluminum is available to be deposited into tissues [1▪].

ALUMINUM CONTAMINANTS IN PARENTERAL NUTRITION SOLUTIONS

Since the 1980s, aluminum contamination of parenteral nutrition additives has been a recognized problem. The majority of evidence supporting the need to reduce aluminum exposure, however, is more than 30 years old. Earlier studies estimated the daily aluminum intake to be 3–4 μmol/kg/day, 50–100 times higher than the estimated mean intake using currently available products [1▪]. Supporting evidence consisted mainly of case reports or small studies, implying that other additives apart from those addressed by the FDA mandate could also contribute to aluminum loading.

PATIENTS AT RISK

Three groups have emerged as being at risk for developing aluminum toxicity: parenteral nutrition-dependent patients, plasmapheresis patients receiving large amounts of albumin, and burn patients receiving large amounts of albumin to maintain oncotic pressure [1▪]. The patients at greatest risk, however, are those with renal insufficiency, especially premature infants [1▪,2▪]. Toxicity appears to be inversely related to gestational age. In addition to having immature renal function, premature infants are more prone to aluminum toxicity because of their increased calcium and phosphorus requirements, two additives known to be rich in aluminum contaminants [1▪]. Conversely, because of their reduced calcium and phosphorus needs, along with an overall larger body size, parenteral nutrition-dependent adolescents and adults do not appear to be significantly impacted by aluminum contaminants as neonates [1▪]. Older patients receive approximately 2 μg/kg/day of aluminum compared with 10–20 μg/kg/day seen in neonatal studies [2▪]. Geriatric patients may also be at risk. With advancing age, aluminum absorption becomes more efficient; thus toxicity may not be the result of renal insufficiency but rather due to a weakened gastrointestinal protective barrier [8▪].

The fetus is also susceptible to aluminum contamination [1▪]. Once maternal aluminum is absorbed, it is transferred transplacentally and accumulates in fetal tissue. Aluminum competes with essential trace elements whose requirements are greatest during periods of rapid growth and development, such as during the last trimester of pregnancy or in early infancy. In utero, fetal malformations, delayed ossification, growth, and impaired neurodevelopment can occur. Aluminum does not appear to transfer into breast milk in any appreciable quantities. In animal studies, less than 2% of a daily dose reaches breast milk [1▪].

COMPLICATIONS OF ALUMINUM TOXICITY

Depending upon the duration of exposure and the amount of aluminum that is present in the systemic circulation, resulting complications will vary dramatically. All organ systems can potentially be impacted.

Metabolic bone disease

Aluminum impacts bone development via a variety of mechanisms [1▪,2▪]. Mineralization is impaired when high levels are present in bone tissue. Aluminum impacts bone mineralization by affecting

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the renal enzyme 1,25-dihydroxyvitamin D-1-alpha hydroxylase, thereby decreasing the conversion of 25-hydroxyvitamin D, the major circulating form of vitamin D, to its biologically active form, 1,25-dihydroxyvitamin D [9▪▪]. Aluminum impairs the bone's uptake of calcium, thus interfering with osteoblast proliferation [1▪,2▪]. Through its binding to phosphorus, aluminum acts directly on bone by inducing a state of phosphate deficiency [1▪]. Bone remodeling becomes compromised by aluminum indirectly by becoming deposited into the parathyroid gland, inhibiting parathyroid hormone secretion [1▪,8▪]. Patients with aluminum loading due to parenteral nutrition have lower serum concentrations of parathyroid hormone than those receiving parenteral nutrition with little or no aluminum exposure.

Metabolic bone disease (MBD) is a well known complication of prolonged parenteral nutrition use, first reported in 1982 [1▪]. MBD secondary to aluminum contamination affected up to 84% of patients receiving home parenteral nutrition for more than 6 months. Signs and symptoms included hypercalciuria, increased serum alkaline phosphatase levels, and severe bone pain [1▪]. Serum aluminum levels typically exceed 30 μg/l and stains show aluminum 30% of the trabecular bone surface [2▪]. Patchy osteomalacia may be evident in bone biopsies. In infants, the onset of MBD is more rapid and can occur within 3 weeks of initiation of parenteral nutrition [9▪▪]. Subsequent research linked the aluminum contamination with common parenteral nutrition additives such as calcium and phosphorus salts, and heparin [2▪]. The extent of bone turnover appears to be related to duration of parenteral nutrition use. In almost all patients receiving long-term parenteral nutrition (that is, parenteral nutrition use >1 year), serum osteocalcin was in the low or low–normal range indicative of a low bone formation rate [1▪,9▪▪]. Accumulation occurred at the mineralization front of bone, which was attributed to aluminum toxicity [1▪]. High serum aluminum concentrations have also been observed without any accumulation in bone. For example, neonates receiving parenteral nutrition for 3 weeks did not experience a decrease in bone formation, provided the average intake of 0.1 to 0.2 μmol/kg/day was not exceeded [1▪]. Similar reports have been observed in adults receiving prolonged courses of parenteral nutrition [10▪▪]. Osteoporosis and the resulting fracture risk are typified by the depletion of bone mineral mass, along with the deterioration of bone microarchitecture [11].

Given there is no cure, early identification of causative factors is important as it may minimize the risk of osteoporosis. There is a strong link that early aluminum exposure in life subsequently impacts peak bone mass. Bone mineral density (BMD) follows childhood and adolescent growth rates into adulthood. Increased fracture rates have been linked with reduced peak BMD, suggesting that childhood BMD may be one of the best indicators of fracture risk later in life, particularly in females [9▪▪]. The significance of early aluminum exposure on bone health was reported by Fewtrell *et al.* [12]. As part of their 15-year follow-up of their landmark study of aluminum exposure in premature infants receiving parenteral nutrition, they noted that aluminum exposure impaired long-term bone mineralization. Infants receiving aluminum-depleted parenteral nutrition had significantly higher bone mineral content (BMC) of the lumbar spine, independent of body or bone size; the hip bone mineral content decreased by 7.6% in children whose aluminum exposure exceeded 55 μg/kg/day. These findings support the premise that early aluminum exposure can lead to the development of long-term complications, such as osteoporosis and hip fracture.

More recently, the impact of aluminum toxicity was investigated as it relates to growth. A recent cross-sectional study comparing pediatric patients with parenteral nutrition-dependent intestinal failure with age-matched, sex-matched, and race-matched controls to determine whether BMC and BMD was lower in the intestinal failure cohort than in healthy controls and to identify potential causative factors [9▪▪]. They found that in intestinal failure PN-dependent patients, BMC was 15% and BMD was 12% lower than in controls. Furthermore, intestinal failure patients had higher serum aluminum concentrations (23 vs. 7 μg/l), higher 25-hydroxy vitamin D concentrations (40 vs. 30 ng/ml), and lower parathyroid hormone concentrations (51 vs. 98 pg/ml) than controls. The authors concluded growth was negatively impacted by excessive aluminum exposure.

Anemia

The potential for hematologic complications of aluminum exposure is closely related to a patient's iron stores. Iron deficiency anemia is an often unrecognized confounder of aluminum toxicity. As much as 90% of all aluminum binding is with the iron transport protein transferrin, which also serves as the primary aluminum-binding ligand [13]. When iron is bound to transferrin, the affinity of transferrin for aluminum is reduced. Provided that there are adequate iron stores, elevations in plasma aluminum concentrations will not result in the displacement of transferrin-bound iron, thereby reducing the potential for toxicity. Aluminum inhibits erythropoiesis and iron metabolism by obstructing

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hemoglobin synthesis and erythroid cell maturation. Because of its binding to transferrin, hypochromic microcytic anemia that is refractory to erythropoietin has been observed in patients with aluminum toxicity [13]. Patients may have mild hypochromic, ferropenic, and microcytic anemia. An increased reticulocyte count may also be present.

Neurologic complications

The neurotoxic properties of aluminum were first recognized more than 100 years ago [1▪]. Specific neurologic complications include memory loss and ataxia. Aluminum-associated dialysis encephalopathy was first described in 1976 and has been essentially eliminated with the introduction of reverse osmosis water purification systems and the availability of aluminum-free phosphate binders [1▪].

Parenteral nutrition-associated aluminum neurotoxicity is also a concern. Aluminum interferes with the uptake of trace elements and may contribute to developmental delay [14]. Transferrin receptors present in the capillaries of the brain aid in the uptake of transferrin-bound aluminum to cross the blood–brain barrier and be deposited [1▪,2▪]. In one study of 227 preterm infants of more than 34 weeks' gestation evaluated for the impact of aluminum exposure from parenteral nutrition, infants receiving aluminum-rich parenteral nutrition solutions (approximately 45 μg/kg/day) for 10 days had a 10-point deficit in their Mental Developmental Index scores and were twice as likely to have scores below 88 [15]. These scores were compared to age-matched controls who received parenteral nutrition solutions that contained 4 to 5 μg/kg/day of aluminum for a comparable time period. Unfortunately, although this study served as the impetus for the establishment of the FDA aluminum mandate, the researchers based their conclusions solely on the aluminum content of the parenteral nutrition additives and did not consider other sources of aluminum, nor did they assess urine or serum aluminum concentrations to determine if there was indeed toxicity present.

Aluminum toxicity has also been associated with structural and physiological ocular damage [16]. Rats given excessive amounts of parenteral aluminum demonstrated prominent retinal changes including photoreceptor cell damage [1▪]. Theoretically, aluminum contamination may exacerbate retinal abnormalities that are often present in premature infants.

Similar to the neurodevelopmental delays seen in neonates, recent evidence suggests that prolonged exposure to aluminum can lead to neurodegeneration and may actively promote the onset and progression of Alzheimer's disease [17▪]. Low levels of aluminum exposure over prolonged periods of time may lead to excess inflammatory activity within the aging brain, leading to neurologic impairment.

Parenteral nutrition-associated liver disease

In addition to the aforementioned complications, aluminum toxicity has been shown to increase the risk of parenteral nutrition-associated liver disease (PNALD) [1▪]. The exact mechanism is not known, although research has shown that at excessive doses, parenterally infused aluminum, can cause hepatic injury similar to that seen in PNALD. In a porcine model, it was shown that the duration of aluminum exposure directly correlated with serum total bile acids and hepatic aluminum concentrations [18]. Marked blunting of bile canaliculi microvilli, a common structural change seen in cholestasis, was observed in hepatic tissue in aluminum-exposed piglets but not controls. As these microvilli are the site of bile acid transporter proteins important in bile secretion, any damage to the microvilli results in a loss of these transporter proteins and a reduction in bile flow [19]. Premature infants may have pre-existing abnormalities in bile acid metabolism; thus, any loss of bile acid proteins secondary to microvilli damage may increase the risk of PNALD. Furthermore, developmental differences in bile acid transporter activity may explain the variation in the severity of PNALD among infants of similar gestational age and feeding history [18].

Another way aluminum exposure can promote hepatoxicity is through its role as an intracellular reactive oxygen species generator that triggers a metabolic shift toward lipogenesis in the hepatocytes [20]. Aluminum may reduce L-carnitine production that interferes with the beta-oxidation of fatty acids within the mitochondria. This can result in dyslipidemia, and fat can accumulate in the liver and lead to cholestasis. This may also play a factor in the neurologic complications seen in aluminum toxicity as similar metabolic derangements may occur within the astrocytes [1▪].

PARENTERAL NUTRITION ADDITIVES ASSOCIATED WITH ALUMINUM CONTAMINATION

The typical additives used in parenteral nutrition compounding have some degree of aluminum contamination. Multivitamins, trace elements, calcium, and phosphate salts all contain appreciable amounts of aluminum [1▪]. Other additives often administered to patients requiring parenteral nutrition, such

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as heparin and albumin, may also contain considerable amounts of aluminum. Another underappreciated source of aluminum contamination is natural products. Natural products manufactured in China generally had higher levels of aluminum in comparison with those from other countries and can contribute to a patient's overall aluminum burden [21▪].

FACTORS THAT IMPACT ALUMINUM CONTAMINATION

There are numerous factors that influence the extent of aluminum contamination in a parenteral additive. The source of the raw material and container design can influence aluminum content [1▪]. Glass containers and rubber vial stoppers have considerably more aluminum contamination than plastic does. Even the type of fluid packaged in glass will impact the amount of leaching. For example, both calcium and phosphorus salts have a high affinity for aluminum that can enhance leaching. Other factors that impact the extent of aluminum contamination are storage conditions and assigned expiration dates. The longer a product remains in storage, the greater the potential for leaching aluminum from the glass vial into the solution.

Practitioners must continue to consider other potential sources of aluminum contamination in addition to that contributed by parenteral nutrition additives. Depending upon the country, current labeling standards may not require aluminum content to be reported. As would be expected, parenteral medications, because of their route of administration, have the greatest potential for aluminum contamination. In one study evaluating medication use of patients receiving regular dialysis treatments, patients receiving intravenous forms of iron, erythropoietin, and insulin had higher blood aluminum levels in comparison with those patients receiving the same medications via an alternative route of administration or simply avoiding their use [22].

FOOD AND DRUG ADMINISTRATION MANDATE AND IMPACT ON PARENTERAL NUTRITION COMPOUNDING

Since the implementation of the FDA mandate, it has been difficult to achieve the desired goal of parenteral nutrition patients receiving less than 5 μg/kg/day of aluminum. Although the aluminum content included on the manufacturer's label reflects the amount present at the product's expiry, the actual content may be far less if newly manufactured products are used. One study directly assayed the aluminum concentrations of freshly compounded parenteral nutrition solutions and compared this value with the estimated aluminum content based on the manufacturer's label; the actual measured aluminum content was 7–10 times less than the calculated value [23]. In a review of 13 384 parenteral nutrition patient-days of pediatric patients receiving parenteral nutrition, it was found that it was only possible to meet the FDA mandate in patients weighing more than 50 kg; in patients weighing less than 50 kg, it was unachievable [24]. Similarly, a recent study showed a significant decrease (40–44%) in aluminum exposure in neonates when the least contaminated additives were used to formulate a parenteral nutrition, but they still were unable to achieve the desired FDA 'safe' limit of less than 5 μg/kg/day [25].

Additional research has been conducted to determine if newer products manufactured since the establishment of the FDA aluminum mandate have impacted aluminum levels in patients. In 2009, Popinska *et al.* [26] assessed aluminum concentrations in children receiving long-term parenteral nutrition. Serum aluminum concentrations were obtained in 24 patients whose duration of parenteral nutrition exposure ranged from 2 to 14.7 years. Serum levels were then compared to the aluminum content present in the parenteral nutrition additives. In all cases, aluminum intake exceeded the FDA recommendations. There was an inverse correlation between daily intake of aluminum and patient body weight and age as smaller, younger patients had higher calcium intakes (due to their higher requirements) in comparison with older children.

CONCLUSION

Unlike the rapid response to eliminating aluminum toxicity in the dialysis patient population, similar successes have not been realized in patients receiving parenteral nutrition. Product formulation changes are slow to emerge from the manufacturers. It remains the responsibility of practitioners to recognize the patient populations at risk for toxicity and act accordingly. Monitoring aluminum status and purchasing products known to possess the least amount of aluminum are two such approaches. The need to balance the risk of developing neurologic disease, hepatotoxicity, metabolic bone disease, and other complications due to aluminum toxicity vs. suboptimal calcium and phosphate intake in parenteral nutrition must also be considered whenever attempts are made to reduce aluminum load. Additional research in this area continues to be warranted.

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None.

Conflicts of interest

Dr Gura is a member of the pharmaceutical advisory board for Alkymos Inc., Lexington, KY, USA.

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- ■ of special interest
- ■■ of outstanding interest

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