# Treatment and prevention of aluminium toxicity

**J. W. Coburn**

Medical and Research Services, West Los Angeles Veterans Affairs Medical Center (Wadsworth Division), and Department of Medicine UCLA School of Medicine. Los Angeles, California.

Patients with impaired or absent renal function are susceptible to aluminium toxicity because: 1) aluminium entering the body is not excreted by normal kidneys, 2) excess aluminium is poorly cleared by standard dialysis, and 3) parenteral loading with aluminium can occur via dialysate with both hemo- or peritoneal dialysis. With current practices, there remains a small risk that aluminium loading can occur via dialysate if water purification fails or if the aluminium content of water increases markedly to exceed the capacity of the water purification system. Also, oral aluminium intake may occur without knowledge of those caring for the patient and/or ingested aluminium may be absorbed with great efficiency, usually from concomitant citrate intake.

## General management principles

The management of aluminium toxicity depends on the type of toxicity present (Table I), but certain important principles include: 1) identifying the source of aluminium; 2) eliminating all sources of aluminium loading, 3) minimizing factors in the patient that augment the pathogenicity of aluminium, and 4) enhancing removal of aluminium from the body in the safest way.

### *Use of Deferoxamine*

Original observations suggested that small and presumably insignificant amounts of aluminium were removed by dialysis procedures due protein-binding of aluminium. Deferoxamine (DFO) was found to chelate aluminium and enhance its removal from the body[1] by forming an ultrafilterable or ultrafiltrable aluminium-DFO complex (aluminoxamine), molecular weight, approximately 600 daltons; this complex is removed by hemodialysis, albeit with only modest efficiency using cuprophane® dialyzers (dialyzer clearance, 20-30 ml/min[2]). Twelve to 24 hours after infusing DFO to an aluminium-loaded patient, the increment in plasma aluminium approximates the rise in ultrafilterable aluminium[2]; adding DFO to blood *in vitro* fails to augment ultrafilterable aluminium. Thus, DFO enhances extraction of aluminium from tissues into the plasma with insignificant displacement of protein-bound aluminium from transferrin[3]. The dialysis of aluminium is greatly augmented by DFO, but three to five hemodialysis procedures are needed using cuprophan membranes to return plasma aluminium to the pre-DFO level. After dialysis with a «high flux» polysulfone dialyzer, plasma aluminium falls after 2-3 hours to the pre-DFO level[4]; adding a sorbent cartridge also augments aluminium clearance[5]. Following weekly DFO infusions, the pre-DFO plasma aluminium levels gradually fall unless aluminium loading continues, e.g. from dialysate or aluminium gels. With repeated DFO infusions and aluminium removal via hemo- or peritoneal dialysis, clinical symptoms of aluminium toxicity often improve[1,6,7]. With aluminium bone disease (ABD), serum calcium levels often fall and serum PTH levels rise. There is a biphasic change in alkaline phosphatase, rising initially followed by a decline toward normal. Bone pain decreases or disappears, muscular weakness improves, and bone biopsies show reduced aluminium staining and improved osteomalacia and bone formation rates[8]. With dialysis encephalopathy, some patients show significant symptomatic improvement but others progress despite DFO therapy[1].

### *Side Effects of Deferoxamine*

With such beneficial effects, why not give DFO to all patients with aluminium toxicity? The magnitude and severity of certain side effects, particularly the potential for fatal infections, preclude DFO use except in patients with life-threatening or severe toxicity that does not respond to other treatment.

Another side effect is hypotension, particularly when 2-3 grams are give i.v. over les than 60-90 minutes; this blood pressure responds to slowing the infusion rate. Acute allergic reactions and thrombocytopenia have occurred. Disturbed visual and/or auditory acuity, often but not always reversible, can occur, particularly with doses exceeding 30-40 mg/kg. These problems emphasize the importance of giving the lowest dose possible.

The most serious potential side effect is the occurrence of fatal mucormycosis in significant numbers of dialysis patients receiving DFO therapy[9]. The mucormycosis developing in DFO-treated dialysis patients develops rapidly, is commonly rhinocerebral or disseminated, and is usually fatal after a brief course (Fig. 1). Most cases are not sus-

Correspondence: Jack W. Coburn, MD.
Nephrology Section (W111L).
Wilshire & Sawtelle Blvds.
Los Angeles, CA 90073.

**Table I.** Types of aluminium toxicity and their features

| Type of toxicity | Features | Comments |
|---|---|---|
| Aluminium Bone Disease (ABD):<br>Osteomalacia.<br>«Aplastic» bone. | Fractures.<br>Bone pain.<br>Hypercalcemia. | *Criteria* > 25 % surface staining and low BFR.<br>Epidemic and endemic forms [21]. |
| Proximal myopathy. | Proximal muscular weakness. | Often coexists with ABD. |
| Dialysis encephalopathy. | Speech abnormality.<br>Personality changes.<br>Temporal lobe symptoms.<br>Symptoms intermittent. | Symptoms often worse immediately after dialysis.<br>Characteristic EEG. |
| Acute aluminium intoxication [17]. | Obtundation.<br>Seizures.<br>Coma (often fatal).<br>Serum Al > 200-300 µg/l. | *Risk factors:*<br>D-Al > 100-200 µg/l.<br>DFO therapy of severe Al toxicity [19].<br>Intake of both citrate plus Al-gel [18]. |
| Cardiomyopathy. | Not defined. | (See text) |
| Aluminium loading without symptoms. | None. | Recognized by:<br>High S-Al;<br>High «Delta» after DFO test [22]; or<br>High bone Al content. |
| Microcytic anemia, not due to iron deficiency. | Microcytosis (normal iron stores). | |

Abbreviations: BFR, bone formation rate; DFO, deferoxamine; S-Al, serum aluminium; D-Al, dialysate aluminium; «Delta», increment in S-Al after DFO; Aluminium, 27 µg/l = 1.0 µmol/l.

pected during life but only detected at postmortem examination; many cases are missed and its incidence in dialysis patients receiving DFO is unknown. The mechanism for increased susceptibility is enhanced virulence of the microorganism due to increased uptake of iron chelated by DFO, a natural microbial siderophore [9, 10]. Dialysis patients are more susceptible than DFO-treated, non-uremic patients receiving DFO for hematologic disorders because feroxamine has a longer «half life» in the renal patient, where its removal depends on dialysis rather than the rapid normal renal mechanisms.

When DFO therapy is essential in a dialysis patient, it would seem safest if several guidelines were followed: The lowest possible DFO dose should be used, e.g., 250 to

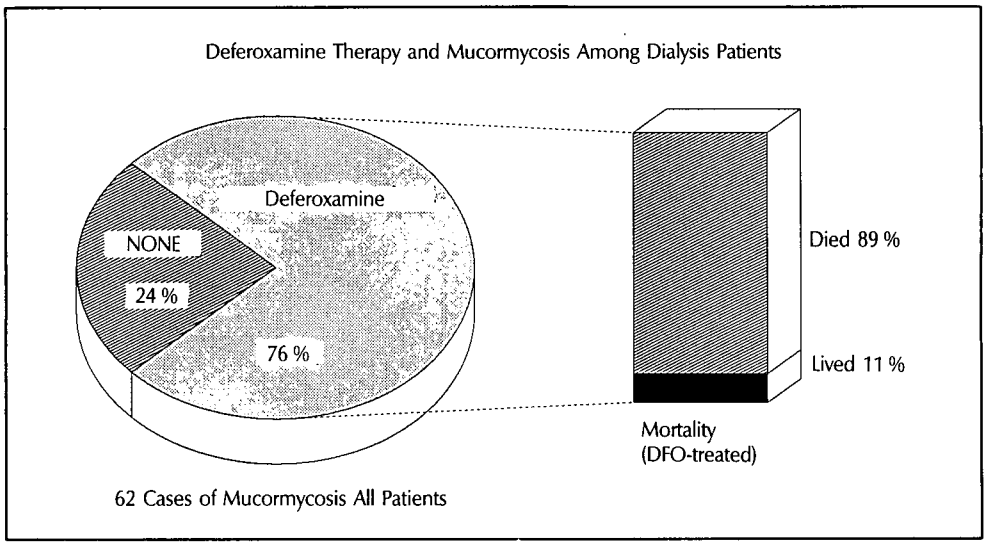


*Fig. 1.—Prevalence of deferoxamine therapy among 62 dialysis patients who developed mucormycosis; there was a very high mortality among these patients receiving deferoxamine (DFO). Adapted from Boelaert et al.[9].*

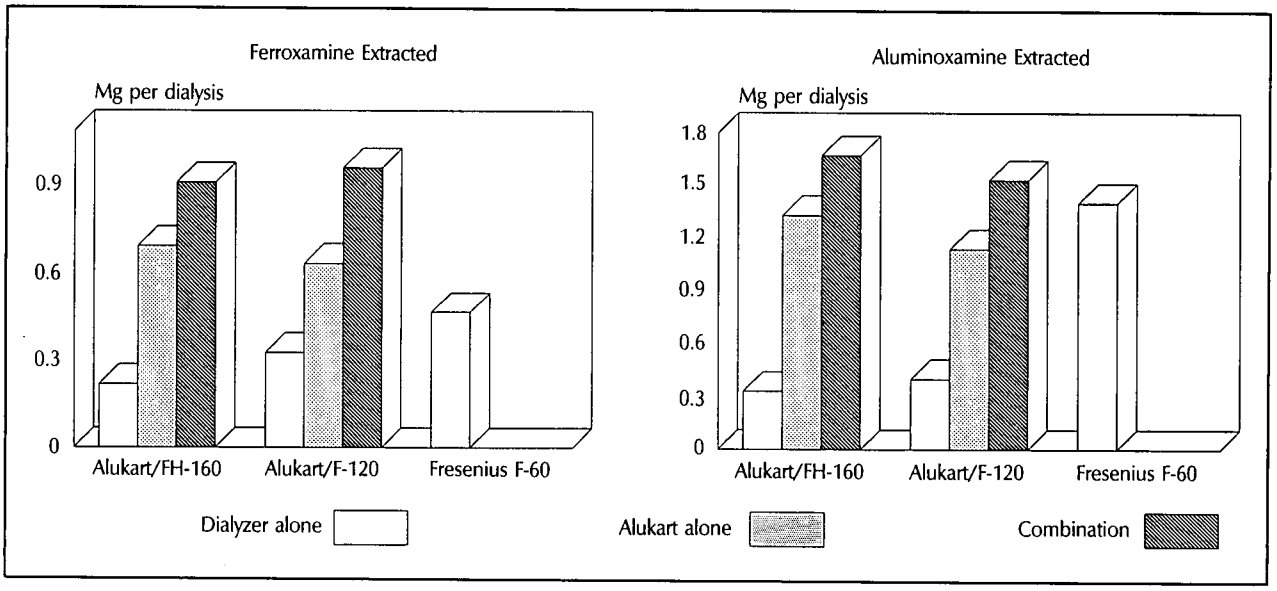


*Fig. 2.—Total amounts of aluminoxamine and ferrioxamine extracted after a dose of deferoxamine during three different set-ups for dialysis, each of which were done in 6 patients in different order and separated by at least 2 weeks. Hemoperfusion was done with the AluKart® charcoal hemoperfusion apparatus in combination with dialysis with both the FH-160 high efficiency 1.62 m² Hemophane® membrane and the F-120 (1.20 m²) standard cuprophane membrane; an additional dialysis without hemoperfusion was done with the F-60 high flux, polysulfone dialyzer. The numbers represent the harmonic means for 6 studies. Adapted from Vasilakakis et al.[12].*

500 mg/week; ideally, it should be given intramuscularly 8-12 hours before dialysis to optimize aluminium chelation (and that of iron) but only a short time before the chelates will be removed by dialysis[11]. Dialysis should be done using a «high flux» dialyzer combined with a sorbent charcoal cartridge (Alucart®, a combination removing both aluminoxamine and feroxamine most rapidly[12], as is shown in Figure 2. With dialysis done 8-10 hours after giving DFO intramuscularly, the patient's exposure to high feroxamine levels would be minimized. The safety of this therapeutic plan is unproven, and the safest choice is not to give DFO except when there is no alternative, as addressed below.

### *Elimination of aluminium exposure*

Most reported trials of DFO therapy were in patients using dialysate with relatively low aluminium levels (< 20 µg/l) and as aluminium gels were continued. With recognition of the pathogenic role of oral aluminium gels[13] and wide introduction of phosphate-binding agents that contain no aluminium[14], alternatives to DFO are available. The combined use of aluminium-free dialysate (< 5-10 µg/l) *and* total withdrawal of aluminium-containing drugs in aluminium-loaded patients permits assessing the efficacy of total aluminium withdrawal. When dialysis patients with aluminium loading or features of aluminium toxicity are totally withdrawn from aluminium exposure, serum aluminium levels and the increment in plasma aluminium after a DFO infusion fall and the histologic features of aluminium toxicity on bone biopsy either disappear or improve substantially[15]. Thus, the total removal of ESRD patients from aluminium exposure results in substantial improvement of aluminium-related bone disease. The experience with such management of aluminium overload is less than with DFO therapy; such inexperience has occurred, in large part, due to the rarity of aluminium toxicity among dialysis patients managed without exposure to aluminium.

### *Role of citrate to augment aluminium absorption*

An important aspect of managing and preventing aluminium toxicity is awareness that citrate markedly enhances aluminium absorption; this occurs with citric acid, sodium citrate, calcium citrate, etc. The augmentation of aluminium absorption is marked —e.g., increases 6-to 20-fold[16]. Citrate ingestion, unknown to the physician or from a source not known to contain citrate (e.g., AlkaSeltzer®), can produce severe aluminium toxicity from oral aluminium gels. Many if not all the patients developing aluminium toxicity before needing dialysis probably received citrate concomitantly[16]. The sources include Shohl's solution or Bicitra® (given to treat metabolic acidosis), calcium citrate (recommended as a phosphate binder), certain over-the-counter preparations, such as AlkaSeltzer®, and the excessive intake of orange juice. The latter occurred in a CAPD patient «addicted» to orange juice but not requiring fluid restriction. No other factor increases aluminium absorption to the degree produced by citrate, and

a careful inquiry into sources of citrate is important when one encounters aluminium toxicity. When aluminium hydroxide, aluminium carbonate, or sucralfate is absolutely required by a dialysis patient, the patient must be warned to avoid all citrate-containing compounds. When citrate is being ingested, it should be discontinued and plasma aluminium levels should be followed serially.

*Elimination of situations predisposing to aluminium toxicity*

- Acute aluminium toxicity

The rapid elevation of plasma aluminium to levels above 200 to 300 μg/l can be associated with the appearance of acute central nervous system (CNS) toxicity[17]. This occurs when dialysis patients are exposed to very high aluminium levels in dialysate, when aluminium absorption is markedly enhanced by citrate[18], or when DFO treatment is started in a patient with marked aluminium overload, leading to markedly elevated plasma aluminium levels[19]. Whether the acute CNS toxicity arises from the very high plasma aluminium levels or whether some intrinsic factor, such as aluminium chelation by citrate or DFO, enhances aluminium movement into the CNS and precipitates the toxicity is unknown. When such toxicity develops during DFO therapy, the CNS symptoms have reversed when DFO was stopped temporarily and later restarted at a lower dose (e.g., ≤ 250 mg/week)[19].

- Toxicity affecting bone

A preexisting state of low bone turnover or abruptly lowering the PTH level with consequent reduced bone turnover enhances the toxic effect of a given body burden of aluminium. On the other hand, the presence of a high bone turnover-state, such as severe hyperparathyroidism, largely prevents a toxic action of aluminun on bone[20]. Thus, patients who have had a previous parathyroidectomy, those with diabetes mellitus, which is more commonly associated with low bone turnover, or those who received glucocorticoid therapy (with an effect to decreased osteoclast function) are at greater risk to develop aluminium bone disease after exposure to aluminium[21]; hence, such patients should avoid aluminium gels or carafate.

When a nephrologist encounters a patient with biochemical evidence of both hyperparathyroidism and aluminium loading, initial efforts should be directed toward treating aluminium toxicity, with later attention to the hyperparathyroidism. For example, in a dialysis patient with a high plasma aluminium level (> 100 μg/l) or a substantial rise in serum aluminium after DFO infusion (increment, > 150 μg/l)[22] combined with an intact PTH level greater than 8-to 10-times normal, overt aluminium toxicity is likely to appear if the PTH levels are reduced first. In such a patients, all aluminium should be withdrawn (both in dialysate and from aluminium-containing gels), and only calcium-containing phosphate-binders should be given until the plasma aluminium levels fall. Calcitriol therapy should not be added unless hypocalcemia appears. If this patient develops *hypercalcemia*, the dialysate calcium should be lowered to 2.5 mEq/l or even as low as 2.0 mEq/l to permit continued use of calcium-containing phosphate binders. If hypercalcemia persists despite this maneuver and if there are symptoms of bone pain and/or muscular weakness, low doses of DFO therapy may be needed for a few weeks or until serum calcium levels fall. After serum aluminium levels are reduced, preferably to below 30-40 μg/l, this patient will be a candidate for pulse-dose calcitriol therapy or parathyroidectomy to manage the secondary hyperparathyroidism. Thus, there should be no rapid reduction of PTH levels until the aluminium burden has dissipated substantially. In this situation, a bone biopsy is useful to identify the presence of significant aluminium staining before parathyroid surgery.

## Management of specific types of aluminium toxicity

There are specific therapeutic considerations for treating the different forms of aluminium toxicity (Table II).

*Aluminium-related bone disease*

If symptoms (fractures, bone pain, or proximal weakness) or hypercalcemia is/are absent, DFO therapy is not justified; all aluminium should be withdrawn and calcium-containing phosphate binders used while dialysate calcium is lowered to 2.5 mEq/l; PTH levels should be reduced cautiously (see above). If hypercalcemia develops, a brief course of DFO therapy may be justified. The dose should be 250 mg every 7 to 10 days with the duration of treatment less than 4-6 months.

If symptoms are present, aluminium should be withdrawn for 5-6 months; if symptoms improve, such therapy should be continued. If no improvement occurs after 5-6 months, a therapeutic trial with DFO, as described above, is justified. Therapy would also be justified if hypercalce-

**Table II.** Management of different types of Aluminium toxicity

| Type | Initial | Chelation with DFO |
|---|---|---|
| Bone disease | Dialysate Al <0.3 nM/l *and* No Al-gels *and* No citrate | Not indicated |
| Encephalopathy | | Add after 5-6 mo |
| Acute Al toxicity | | 250 mg q 8-10 days |
| Anemia | | 250 mg q 8-10 days |
| Asymptomatic | | Not indicated |
| Cardiomyopathy | | Not indicated |
| | | Possibly indicated |

Abbreviation: DFO, deferoxamine.

mia persists despite lower calcium in dialysate and serum phosphorus levels cannot be controlled with calcium-containing binders.

*Proximal myopahty*

Proximal muscular weakness should be managed the same as aluminium-related bone disease: DFO therapy is not justified until after a trial of total aluminium withdrawal; it is imperative that aluminium toxicity be documented by demonstrating significant aluminium staining on bone biopsy before DFO therapy.

*Dialysis Encephalopathy*

The finding of typical dialysis encephalopathy (Tabla I), with the diagnosis confirmed by electroencephalogram and features of aluminium loading, justifies starting DFO therapy. The initial dose should be 250 mg every 7 to 10 days, with high flux dialysis and a sorbent cartridge used after each dose of DFO. If the plasma aluminium levels increase above 400 to 500 μg/l after DFO, the dose of DFO should be reduced and it should be given less frequently[19]. The duration of treatment should be 4 to 6 months or until the patient's symptoms improve.

*Acute aluminium Intoxication*

If this syndrome appears during DFO therapy[19], the DFO should be temporarily stopped and restarted at a lower dose after clinical recovery has ocurred. When this syndrome arises from markedly elevated dialysate aluminium levels or the ingestion of aluminium combined with citrate, these causal factors *must* be remedied. Under such circumstances, low dose DFO therapy should be utilized, but the prognosis is grave and there is no experience indicating that DFO therapy can reverse this syndrome[18].

*Aluminium-related microcytic anemia (Iron deficiency absent)*

This clinical finding would not justify the risk of DFO therapy; all aluminium should be stopped.

*Cardiomyopathy associated with aluminium overload*

If a patient has: 1) aluminium loading, 2) aluminium deposition within the myocardium, and 3) severe cardiomyopathy without any other cause, DFO therapy may be justified; however, there are no data to indicate that such treatment can modify the outcome.

*Aluminium-loading without Clinical Manifestations*

There should be total withdrawal of aluminium exposure; DFO should not be given unless hypercalcemia develops and persists despite lower calcium levels in dialysate.

**Acknowledgements**

Some of the work described in this manuscript has been supported by research funds from the Department of Veterans Affairs.

## References

1. Ackrill P, Ralston AJ, Day JP, Hodge KC: «Successful removal of aluminium from a patient with dialysis encephalopathy». *Lancet* 2:692-693, 1980.
2. Milliner DS, Hercz G, Miller JH, Shinaberger JH, Nissenson AR, Coburn JW: «Clearance of aluminium by hemodialysis. Effect of desferrioxamine». *Kidney Int* 20 (Suppl. 18):S100-S104, 1986.
3. Rahman M, Skillen AW, Ward MK, Channon SM, Kerr DNS: «Affinity of the aluminium binding protein». *Int J Artif Organs* 9:93-99, 1986.
4. Molitoris BA, Alfrey AC, Alfrey PS: «Rapid removal of DFO-chelated aluminium during hemodialysis using polysulfone dialyzers». *Kidney Int* 34:98-101, 1988.
5. Delmez J, Weerts C, Lewis-Finch J, Windus D, Slatopolsky E: «Accelerated removal of deferoxamine mesylate-chelated aluminium by charcoal hemoperfusion in hemodialysis patients». *Am J Kidney Dis* 13:308-311, 1989.
6. Hercz G, Salusky IB, Norris KC, Fine RN, Coburn JW: «Aluminium removal by peritoneal dialysis: Intravenous vs intraperitoneal deferioxamine». *Kidney Int* 30:944-948, 1986.
7. Malluche HH, Smith AJ, Abreo K, Faugere MC: «The use of deferioxamine in the management of aluminium accumulation in bone in patients with renal failure». *N Engl J Med* 311:140-144, 1984.
8. Andress DL, Nebeker HG, Ott SM, Endres DB, Alfrey AC, Slatopolsky EA, Coburn JW, Sherrard DJ: «Bone histologic response to deferoxamine in aluminium-related bone disease». *Kidney Int* 31:1344-1350, 1987.
9. Boelaert JR, Fenves AZ, Coburn JW: «Deferoxamine therapy and mucormycosis in dialysis patients: Report of an international registry». *Am J Kidney Dis* 18:660-667, 1991.
10. Van Cutsem J, Boelaert JR: «Effects of deferoxamine, feroxamine and iron on experimental mucormycosis (zygomycosis)». *Kidney Int* 36:1061-1068, 1989.
11. Molitoris BA, Alfrey PS, Miller NL, Hasbargen JA, Kaehny WD, Alfrey AC, Smith BJ: «Efficacy of intramuscular and intraperitoneal deferoxamine for aluminium chelation». *Kidney Int* 31:986-991, 1987.
12. Vasilakakis DM, D'Haese PC, Lamberts LV, Lemoniatou E, Digenis PN, DeBroe ME: «Removal of aluminoxamine and ferrioxamine by charcoal hemoperfusion and hemodialysis». *Kidney Int* 41: 1400-1407, 1992.
13. Salusky IB, Coburn JW, Paunier L, Sherrard DJ, Fine RN: «Role of aluminium hydroxide in raising serum aluminium levels in children undergoing continuous ambulatory peritoneal dialysis». *J Pediatr* 105:717-720, 1984.
14. Slatopolsky E, Weerts C, López-Hilker S, Norwood K, Zink M, Windus M, Delmez J: «Calcium carbonate is an effective phosphate binder in patients with chronic renal failure undergoing dialysis». *N Engl J Med* 315:157-161, 1986.
15. Hercz G, Andress DL, Norris KC, Shinaberger JH, Slatopolsky E, Sherrard DJ, Coburn JW: «Improved bone formation in dialysis patients after substitution of calcium carbonate for aluminium gels». *Trans Assoc Am Physicians* 100:139-145, 1987.
16. Molitoris BA, Froment DH, Mackenzie TA, Huffer WH, Alfrey AC: «Citrate: a major factor in the toxicity of orally administered aluminium compounds». *Kidney Int* 36:949-953, 1989.
17. Alfrey AC, Froment DH: «Dialysis encephalopathy». En *Aluminium and Renal Failure*, edited by De Broe ME, Coburn JW. Dordrecht, Kluwer Academic Publishers, pp. 249-257, 1990.
18. Bakir AA, Hryhorczuk DO, Berman E, Dunea G: «Acute fatal hyperaluminemic encephalopahty in undialyzed and recently dialyzed uremic patients». *Trans Am Soc Artif Intern Organs* 32:171-176, 1986.

19. Sherrard DJ, Walker JV, Boykin JL: «Precipitation of dialysis dementia by deferoxamine treatment of aluminium-related boen disease». *Am J Kidney Dis* 12:126-130, 1988.
20. Ellis HA: «Aluminium and osteomalacia after parathyroidectomy». *Ann Intern Med* 96:533-534, 1982.
21. Norris KC, Crooks PW, Nebeker HG, Hercz G, Milliner DS, Gerszi K, Slatopolsy E, Andress DL, Sherrard DJ, Coburn JW: «Clinical and laboratory features of aluminium-related bone disease: differences between sporadic and "epidemic" forms of the syndrome». *Am J Kidney Dis* 6:342-347, 1985.
22. Pei Y, Hercz G, Greenwood C, Sherrard D, Segre G, Manuel A, Saiphoo C, Fenton S: «Non-invasive prediction of aluminium bone disease in hemo- and peritoneal dialysis patients». *Kidney Int* 41:1374-1382, 1992.