Aluminium Toxicity In Peritonel Dialysis

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Introduction

- In the general population, exposure to aluminum usually happens through the foodstuffs (processed foods), drinking water, and aluminum-containing medicines, aluminum cookware or cosmetic products (for example antiperspirants, sun creams and toothpaste)
- The intake of aluminum from food and water is relatively little in comparison with aluminum-containing medicines
- Inhalation and ingestion (via food and water) are the two principal routes through which aluminum enters into human body, but aluminum can also be absorbed through the skin

Introduction

- Serum Al is mostly bound to plasma proteins, notably transferrin
- Ultrafiltrable (or unbound) Al in chronic kidney disease is reported to be approximately 20 % of total serum Al, with a range between 10 and 33 %
- Only the unbound fraction of molecules diffuse across an artificial dialyzer and, to a lesser extent, across the peritoneal membrane

Aluminum in dialysis fluid

- The major sources include the dialysis fluid and aluminum-containing phosphate binders
- Patients on hemodialysis are exposed to very large volumes of dialysate water and have no means to excrete the aluminum that is in the fluid
- The toxicity of aluminum in dialysis water has been recognized since the 1970s .
- This recognition led to the development of effective methods of water purification

CLINICAL MANIFESTATIONS

The clinical manifestations of aluminum toxicity may be Chronic or

Acute, depending on the rate and amount of aluminum accumulation

Chronic toxicity

- Manifestations of chronic aluminum toxicity result from exposure to low concentrations over a period of years

- Chronic manifestations include bone and muscle pain, fracture, proximal muscle weakness, osteomalacia, iron-resistant microcytic anemia, hypercalcemia, and slowly progressive dementia

Bone and muscle pain and muscle weakness

- Patients with aluminum toxicity complain of generalized bone and joint pain and proximal muscle weakness.
- The joint symptoms may reflect aluminum deposition within the joint.
- High aluminum concentrations have been observed in synovial fluid
- Joint aspiration is generally not done for diagnosis

Osteomalacia

- Aluminum toxicity used to be the most common cause of osteomalacia in patients with CKD
- Aluminum overload causes defective mineralization, increased matrix synthesis by osteoblasts, inhibition of osteoblast differentiation, and the inhibition of osteoclast function

Hyperparathyroidism

- To protect against aluminum-induced osteomalacia, perhaps by increasing bone turnover
- Parathyroidectomy can lead to worsening of aluminum-induced osteomalacia
- Lowering PTH levels medically by the administration of calcitriol also may accelerate aluminum bone disease

Iron-resistant microcytic anemia

- Accumulation of aluminum in bone marrow causes a reversible microcytic anemia
- The anemia in such patients is resistant to iron supplementation

Hypercalcemia

- Hypercalcemia is caused by aluminum deposition on the mineralization front, which blocks calcium uptake into bone

- Aluminum toxicity should be suspected among CKD patients who have hypercalcemia without marked elevations in serum intact PTH (eg, <500 pg/mL) and are not taking vitamin D or calcium supplements

Dementia

- A slowly progressive dementia (formerly called dialysis dementia) results from prolonged aluminum toxicity.
- Aluminum-related dementia is characterized by dysarthria, myoclonus, mental changes, hallucinations, and seizures

Acute toxicity

- Manifestations of acute aluminum toxicity result from exposure to very high concentrations of aluminum in the dialysate (ie, >200 mcg/L).
- (the maximum allowable limit is 10 mcg/L)
- The major clinical manifestation is acute encephalopathy, which can be fatal
- Acute aluminum-induced encephalopathy is characterized by altered consciousness, seizures, and coma
- The mortality is high

Diagnosis of aluminum intoxication

- The diagnosis of aluminum intoxication should be based on clinical suspicion and laboratory
- The laboratory diagnosis of Al intoxication is confirmed by the presence of elevated serum Al levels (> 100 µg/L) or a positive desferrioxamine (DFO) test (Al post – Al pre DFO ≥ 50 µg/L)
- To consider the DFO test as false positive associated with the context of serum ferritin levels < 100 ng/mL, or false negative if > 500 ng/mL

Diagnosis of aluminum intoxication

- If the DFO test could not be performed, or when a false negative result is suspected, bone biopsy is indicated

- Values greater than 30% of the trabecular surface covered by Al are the gold standard for the diagnosis of bone intoxication by this metal

Screening and diagnosis of aluminum toxicity

- Deferoxamine at a dose of 5 mg/kg be administered one hour prior to the end of the dialysis session
- High doses of deferoxamine (40 mg/kg) have been associated with toxic side effects including irreversible ophthalmologic damage and mucormycosis
- The serum aluminum should be measured prior to and two days after the deferoxamine infusion
- The test is considered positive if there is an increase in serum aluminum of ≥50 mcg/L

Screening and diagnosis of aluminum toxicity

We select patients for deferoxamine-stimulated serum aluminum levels based upon the

serum aluminum level and the presence or absence of typical symptoms

Unstimulated serum aluminum levels <20 mcg/L :

- Aluminum toxicity is unlikely in patients with baseline unstimulated serum aluminum concentrations <20 mcg/L
- Do not require further testing with the deferoxamine stimulation

Screening and diagnosis of aluminum toxicity

Asymptomatic, unstimulated aluminum levels 20 to 60 mcg/L :

- We suggest not performing a deferoxamine stimulation test

- Serum aluminum concentrations should be repeated in one month

Screening and diagnosis of aluminum toxicity

Symptomatic, unstimulated serum aluminum levels 20 to 60 mcg/L :

- We suggest deferoxamine stimulation testing to confirm diagnosis and to guide treatment if the deferoxamine stimulation test is positive

- Patients who have a negative deferoxamine stimulation test should have the unstimulated aluminum concentration rechecked after one month

Screening and diagnosis of aluminum toxicity

Unstimulated serum aluminum levels 60 to 200 mcg/L :

- We suggest deferoxamine stimulation testing, whether or not symptoms of toxicity are present

- Unstimulated serum aluminum concentrations >60 strongly support the diagnosis of aluminum toxicity

Screening and diagnosis of aluminum toxicity

Unstimulated serum aluminum levels >200 mcg/L :

- The deferoxamine test should not be performed

- Administration of deferoxamine causes severe, and occasionally fatal, neurotoxicity

- This is presumed to be related to deferoxamine-induced mobilization of aluminum that has been deposited in tissues, resulting in transiently increased aluminum concentrations in the cerebrospinal fluid

Treatment of aluminum intoxication

- Treatment of Al intoxication regardless of the dialysis modality should be done with DFO at a single dose of 5 mg/kg/ week, intravenously, for 30 to 60 minutes
- For hemodialysis patients, DFO should be administered after the end of the first or second hemodialysis session of the week
- For patients with serum Al levels > 100 µg/L, DFO should be administered 5 hours prior to the start of the first hemodialysis session of the week

Treatment of aluminum intoxication

- For patients undergoing peritoneal dialysis, DFO should be administered intravenously, with an empty abdominal cavity
- On automated peritoneal dialysis (APD), DFO should be administered 5 hours prior to the start of dialysis
- On CAPD, dialysis should only be restarted after a minimum of 5 hours after the end of DFO
- DFO should be discontinued in case of serious adverse events, such as visual and/or hearing disorders, drug-attributed allergy, or opportunistic infections

TREATMENT

- Treatment for aluminum toxicity includes all or some of the following interventions:

A. Identification and removal of all sources of aluminum

B. Intensive (six days per week) dialysis with high-flux dialysis

C. Administration of deferoxamine

Symptomatic patients

Serum concentration 20 to 200 mcg/L :

All symptomatic patients with unstimulated serum aluminum 20 to 200 mcg/L should undergo deferoxamine stimulation testing to determine the optimal treatment

Symptomatic patients

Deferoxamine-stimulated aluminum concentration increase of 50 to 299 mcg/L :

- We give deferoxamine 5 mg/kg weekly for eight doses.
  - Deferoxamine removes aluminum that has been deposited in tissue
- Deferoxamine is generally given intravenously over the last hour of hemodialysis

Symptomatic patients

- We repeat the deferoxamine stimulation test one month after completion of the eight-week course.
- If there is an increase in deferoxamine-stimulated aluminum concentration of 50 to 299 mcg/L, we give eight more weekly doses of 5 mg/kg and repeat the stimulation test after an additional month.
- If, after eight weeks of treatment, the deferoxamine-stimulated aluminum increases by <50 mcg/L, then no further deferoxamine is given.
- The stimulation test should be repeated at one month and again at four months

Symptomatic patients

Deferoxamine-stimulated aluminum concentration increase of ≥300 mcg/L

- We give deferoxamine 5 mg/kg weekly for 16 doses (four months)
  - Deferoxamine is given over one hour, five hours prior to the performance of high-efficiency hemodialysis
- This strategy should maximize removal of the deferoxamine-aluminum complex and minimize side effects

Symptomatic patients

- We repeat the deferoxamine stimulation test one month after the 16-week
- If there is an increase in deferoxamine-stimulated aluminum concentration >300 mcg/L, we give an additional 16 weekly
- If there is an increase 50 to 299 mcg/L, we give an additional eight weekly
- The stimulation test is repeated one month after completion of the eight-week

Symptomatic patients

Serum concentration >200 mcg/L

- Should not undergo a deferoxamine stimulation test
- The administration of deferoxamine causes severe and occasionally fatal neurotoxicity
- This is thought to be related to deferoxamine-induced mobilization of Al causes transient increases in Al concentrations in the cerebrospinal fluid

Symptomatic patients

- This patients should be treated with intensive hemodialysis (six times per week) for four to six weeks or as long as is required for the serum Al concentration to decrease to <200 mcg/L
- A high-flux dialysis membrane should be used to provide the maximum clearance of aluminum
- The dialysis fluid aluminum concentration should be ≤5 mcg/L, which is approximately half the maximum concentration for aluminum allowed by international standards

Symptomatic patients

- If the baseline serum aluminum is reduced to <200 mcg/L after intensive hemodialysis, a low-dose deferoxamine test is performed, with subsequent treatment based upon the results of the stimulation test

Asymptomatic patients

Serum concentration 20 to 60 mcg/L ：

- Do not perform deferoxamine stimulation testing
- We also do not treat such patients with deferoxamine
- All medications that are not absolutely necessary and which may contain small amounts of aluminum should be discontinued

Asymptomatic patients

Serum concentration >60 mcg/L :

- Should be treated the same as patients with similar aluminum concentrations who have symptoms of toxicity

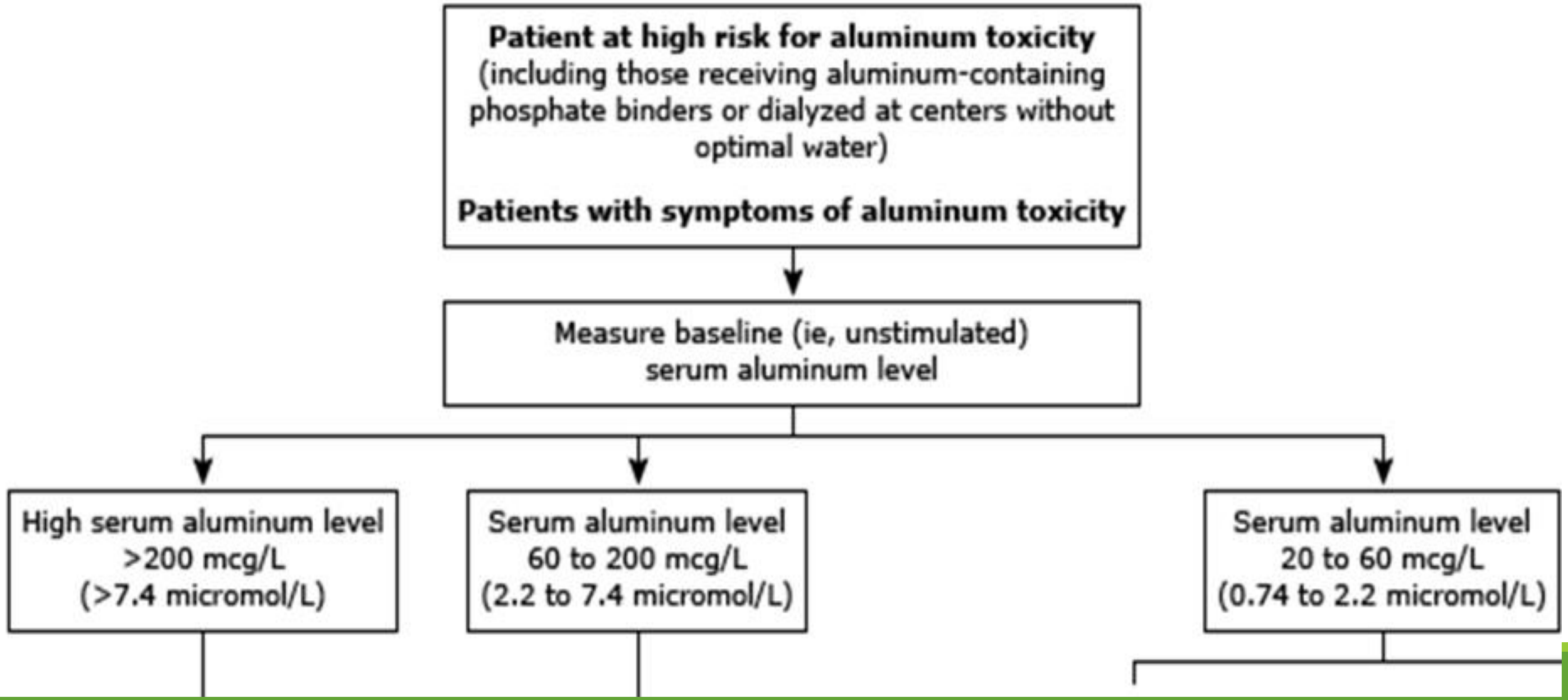
ADVERSE EFFECTS OF DEFEROXAMINE

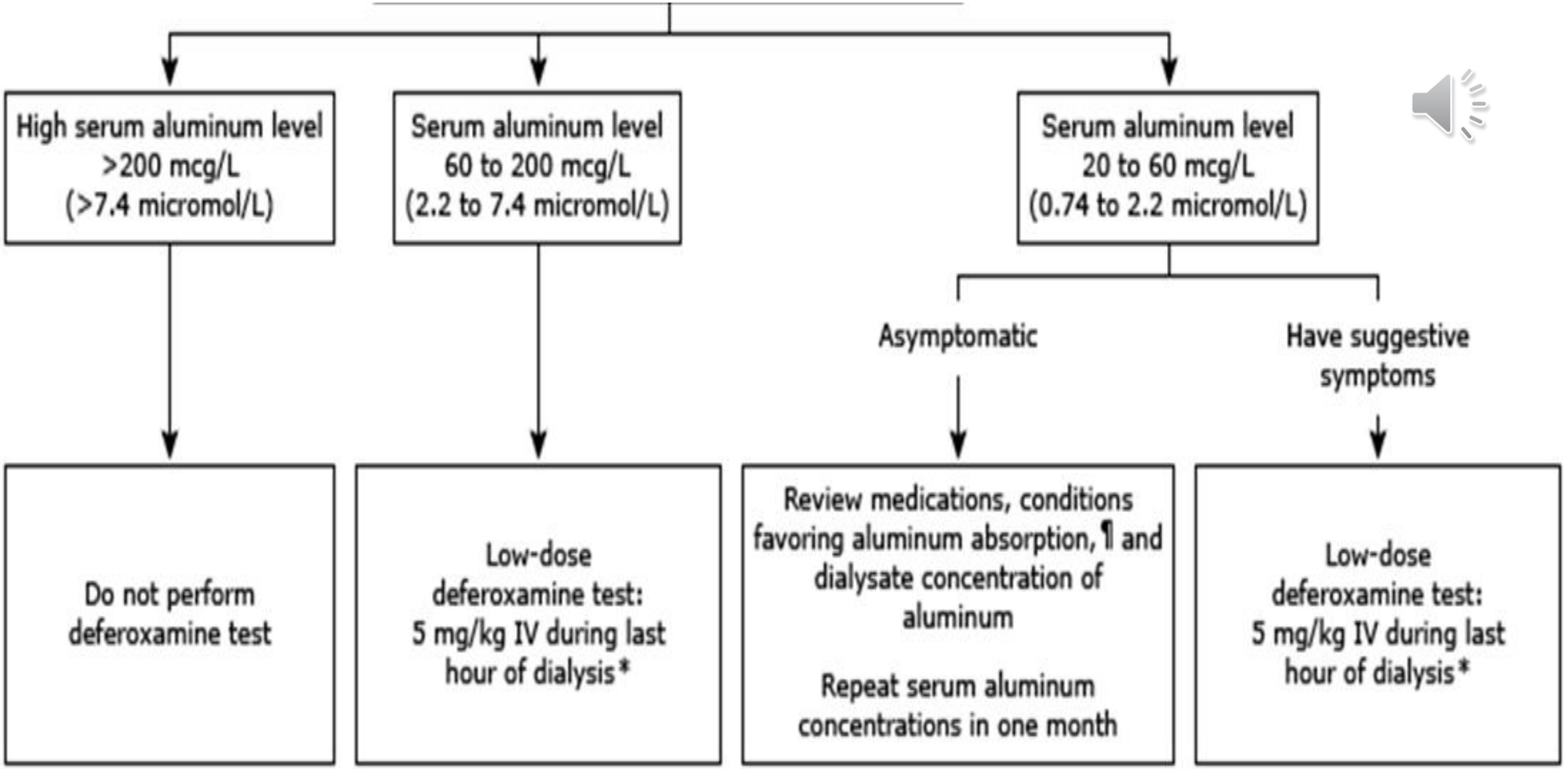
- Major side effects with deferoxamine therapy include neurotoxicity and increased risk of mucormycosis
- Neurotoxicity may result from transiently increased concentrations of aluminum in the cerebrospinal fluid
- Deferoxamine can also cause nausea, pruritus, myalgias, hypotension, and anaphylaxis
- There is an increased risk of adverse effects among patients who have high serum aluminum concentrations or are treated with high doses of deferoxamine

Aluminum removal by peritoneal dialysis:

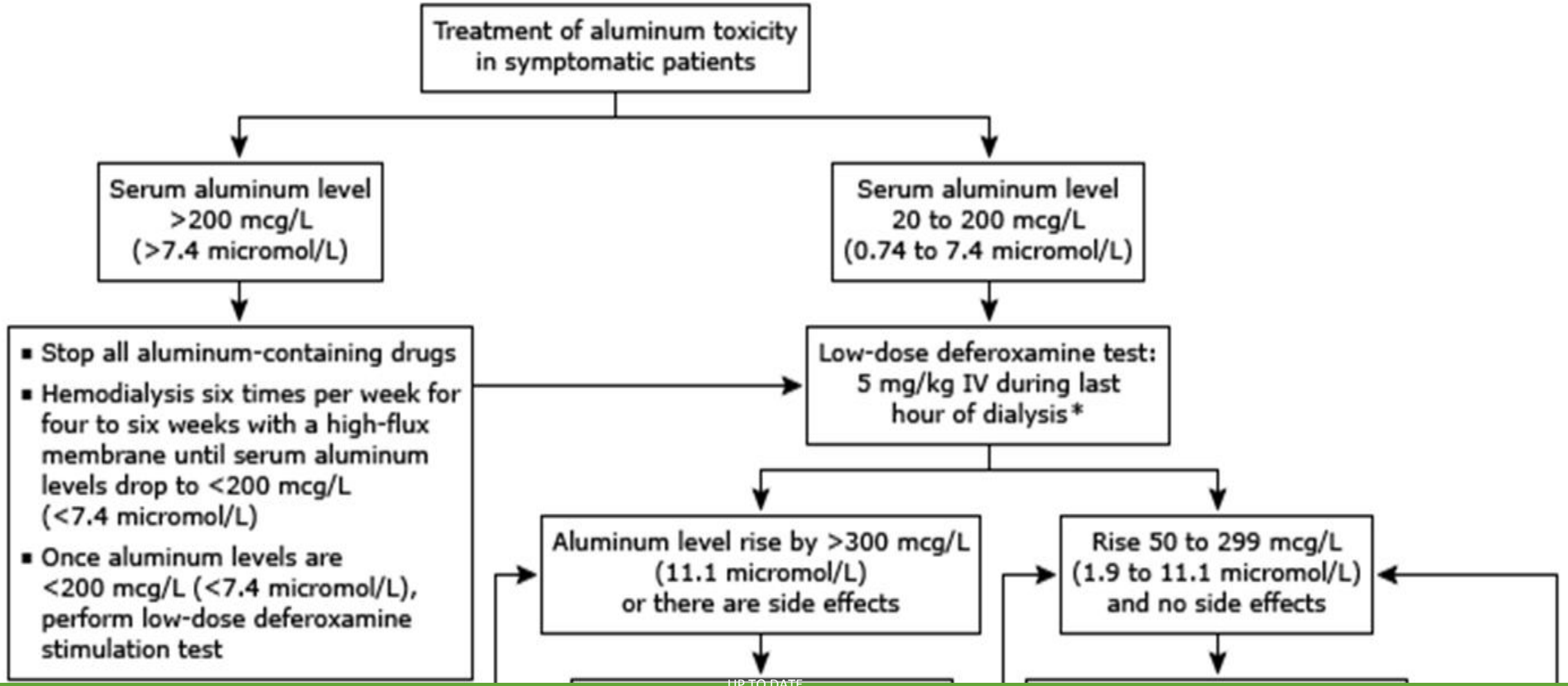
- Aluminum is effectively removed after the administration of either intravenous or intraperitoneal deferoxamine.
- Removal of aluminum by peritoneal dialysis persists for several days after a single dose of deferoxamine
- Intraperitoneal administration of deferoxamine would also be effective in enhancing the removal of aluminum

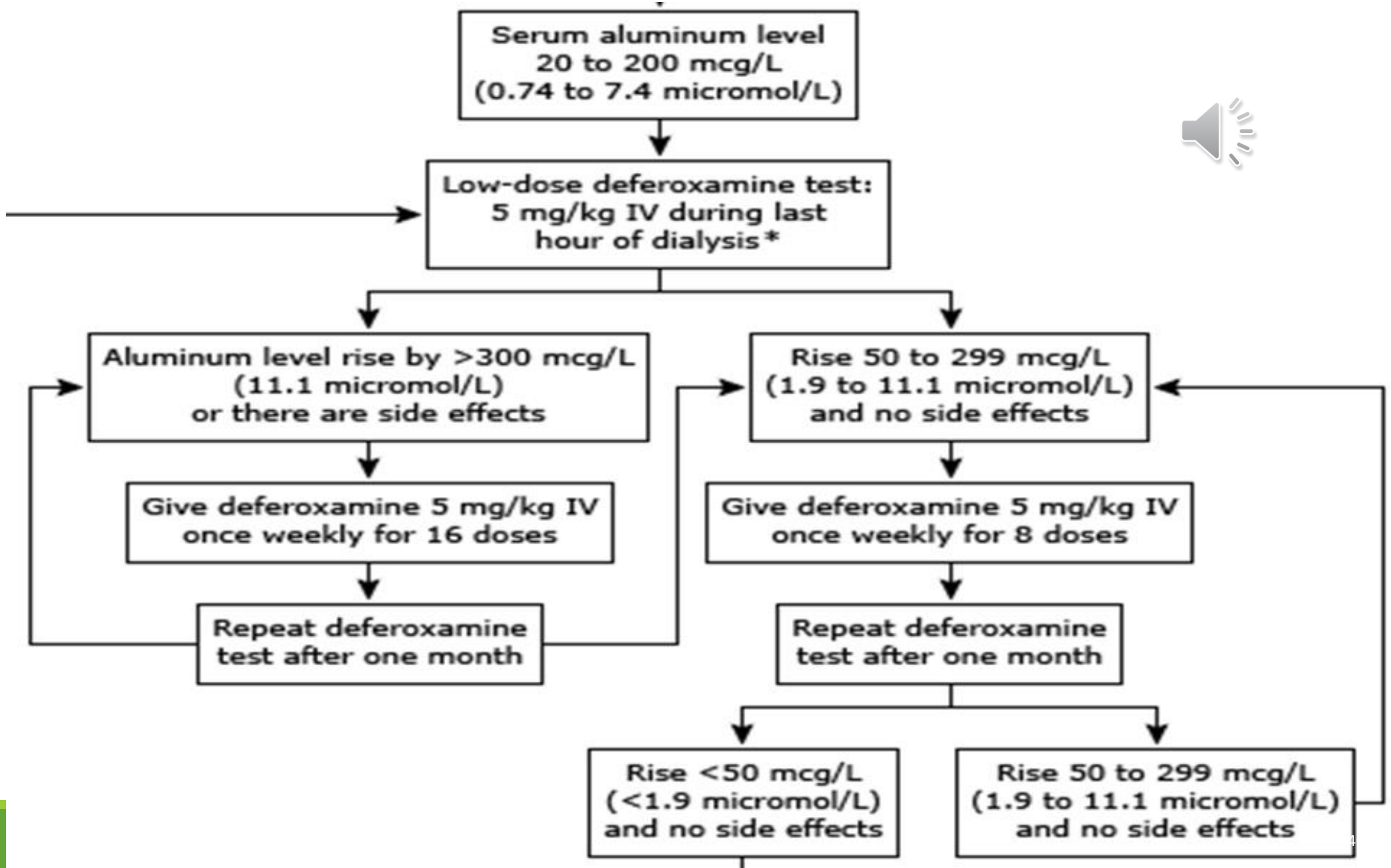
Screening and diagnosis of aluminum toxicity

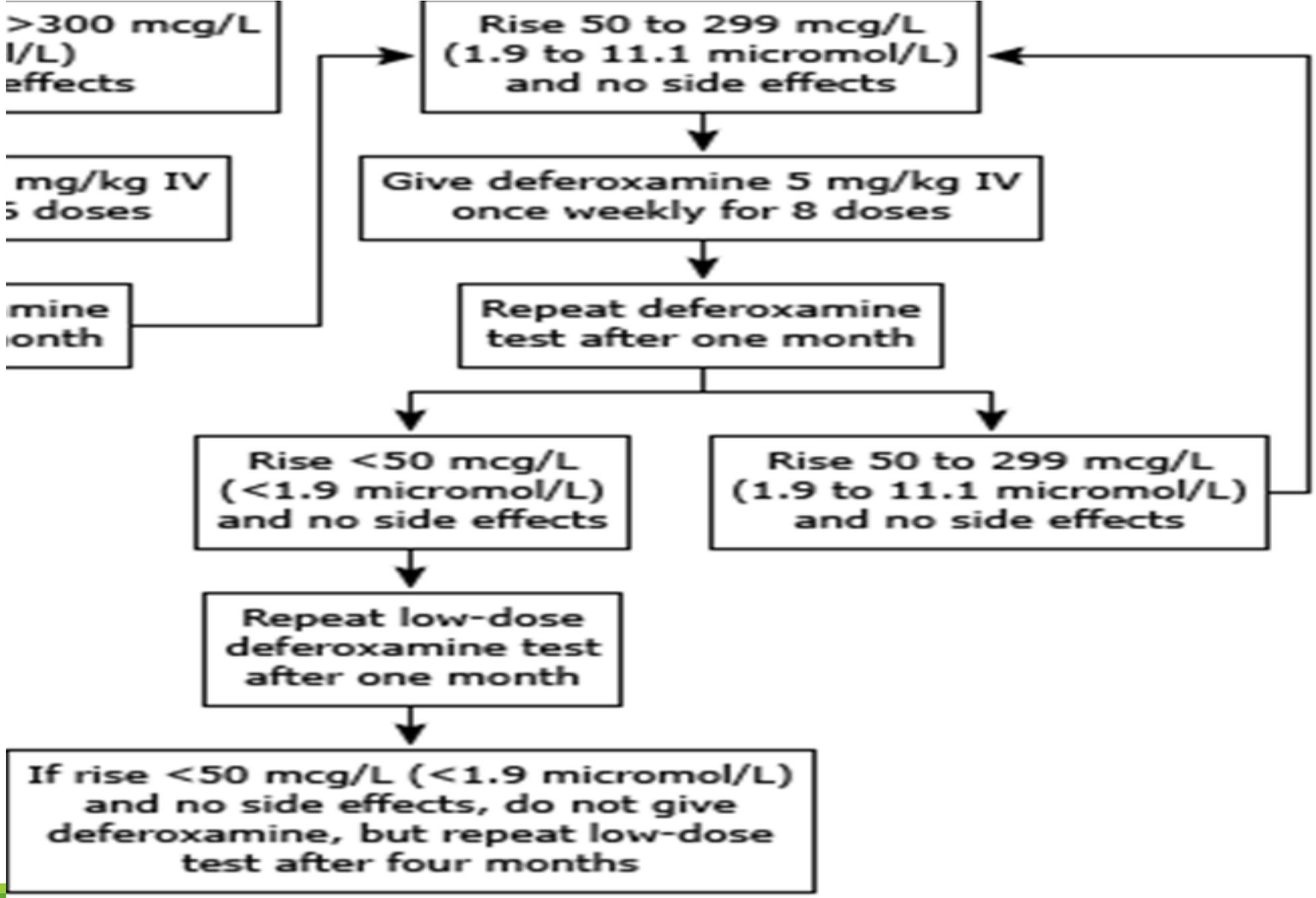



High serum aluminum level
>200 mcg/L
(>7.4 micromol/L)
Serum aluminum level
60 to 200 mcg/L
(2.2 to 7.4 micromol/L)
Serum aluminum level
20 to 60 mcg/L
(0.74 to 2.2 micromol/L)
Asymptomatic
Have suggestive symptoms
Do not perform deferoxamine test
Low-dose deferoxamine test:
5 mg/kg IV during last hour of dialysis*
Review medications, conditions favoring aluminum absorption, ¶ and dialysate concentration of aluminum
Repeat serum aluminum concentrations in one month
Low-dose deferoxamine test:
5 mg/kg IV during last hour of dialysis*

Treatment of aluminum toxicity in symptomatic patients




Serum aluminum level
20 to 200 mcg/L
(0.74 to 7.4 micromol/L)
Low-dose deferoxamine test:
5 mg/kg IV during last
hour of dialysis*
Aluminum level rise by >300 mcg/L
(11.1 micromol/L)
or there are side effects
Give deferoxamine 5 mg/kg IV
once weekly for 16 doses
Repeat deferoxamine
test after one month
Rise 50 to 299 mcg/L
(1.9 to 11.1 micromol/L)
and no side effects
Give deferoxamine 5 mg/kg IV
once weekly for 8 doses
Repeat deferoxamine
test after one month
Rise <50 mcg/L
(<1.9 micromol/L)
and no side effects
Rise 50 to 299 mcg/L
(1.9 to 11.1 micromol/L)
and no side effects


>300 mcg/L
l/L)
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Rise 50 to 299 mcg/L
(1.9 to 11.1 micromol/L)
and no side effects
mg/kg IV
5 doses
Give deferoxamine 5 mg/kg IV
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onth
Repeat deferoxamine
test after one month
Rise <50 mcg/L
(<1.9 micromol/L)
and no side effects
Rise 50 to 299 mcg/L
(1.9 to 11.1 micromol/L)
and no side effects
Repeat low-dose
deferoxamine test
after one month
If rise <50 mcg/L (<1.9 micromol/L)
and no side effects, do not give
deferoxamine, but repeat low-dose
test after four months