5 Disorders of Magnesium Metabolism

Charles P. McKay

Key Points

1. Serum magnesium concentrations may not reflect the state of whole body magnesium stores.
2. In magnesium depletion states, urinary fractional excretion of magnesium should be less than 2% if renal conservation is normal.
3. Hypomagnesemia is a common electrolyte disturbance that is usually mild but can be associated with refractory hypocalcemia and severe neuromuscular and cardiac disturbances.
4. Recently described genetic abnormalities of intestinal and renal magnesium transport are important causes of hypomagnesemia.

Key Words: Magnesium; hypomagnesemia; hypermagnesemia; hypocalcemia; Bartter syndrome

1. INTRODUCTION

Magnesium is the 4th most abundant cation in the body with an average adult having about 25 g of magnesium and the 2nd most abundant cation in the cell. It shares many characteristics with calcium but does not appear to be regulated by a control system like calcium, which is regulated by PTH and vitamin D. The homeostasis of magnesium is largely controlled by the kidney whereas the level of serum calcium is the result of the net flux from bone, intestine, and kidney. Magnesium is a divalent cation with an atomic weight of 24 and serves in the body as an important cofactor for numerous enzymes, especially those involving ATP. It is therefore very important in the regulation of membrane stability, hormone secretion, neuromuscular, and cardiovascular function. Disorders of magnesium metabolism are characterized by abnormalities in these systems.

2. DISTRIBUTION OF MAGNESIUM IN THE BODY

Sixty six percent of all total body magnesium is in the skeleton as compared to 99% for calcium. Another 33% of total body magnesium is intracellular, with the majority being in muscle and liver and only 1% is extracellular *(1)*.

From: *Nutrition and Health: Fluid and Electrolytes in Pediatrics*
Edited by: L. G. Feld, F. J. Kaskel, DOI 10.1007/978-1-60327-225-4_5,

2.1. Serum Magnesium

The normal serum level of magnesium is kept in a fairly constant range of 1.6–2.4 mg/dL (1.4–2 mEq/L or 0.7–1.0 mmol/L) *(2)*. Similar to calcium, it is the ionized portion of magnesium, which is physiologically important and that represents 55–70% of serum magnesium with protein-bound and complexed fractions making up about 20–30 and 10–20%, respectively. Because the relative amount of protein-bound magnesium is about half of that of calcium, the effect of low albumin states on the relation between total and the ionized fraction is not as dramatic with magnesium. Total serum magnesium levels correlate well with symptoms of hyper- and hypomagnesemia but do not correlate well with muscle and other tissue stores but there is better correlation with bone stores.

2.2. Tissue Magnesium

The majority of magnesium is in bone where it resides on the surface of the hydroxyapatite crystals and is freely exchangeable *(3)*. The remaining 2/3 of total body magnesium is intracellular where it lies predominantly in organelles, especially the mitochondria. The cytosolic magnesium has a concentration of about 0.5 mM but is largely complexed to proteins and organophosphates with a small component being ionized. The concentration of intracellular magnesium does not vary greatly in the presence of hypomagnesemia or hypermagnesemia. The control of intracellular magnesium is still poorly described but is linked to cellular potassium homeostasis. Magnesium depletion appears to reduce muscle tissue stores of potassium and vice versa with a fall of muscle magnesium of 0.5 mmol for every 10 mmol fall in muscle potassium.

3. MAGNESIUM HOMEOSTASIS

Normal magnesium balance in adults is the result of ingestion of about 300 mg in the diet with secretion of about 30 mg with digestive juices *(4)*. There is net absorption of 30% or 100 mg, which is usually excreted in the urine. Net magnesium absorption is linear with magnesium intake. Magnesium is plentiful in most foods so dietary deficiency is unusual. The daily requirements for magnesium range from 50 mg in the first 6 months of life to 150–250 mg in young children under 10 years of age to 400 mg in adolescent males. Magnesium absorption is not regulated so magnesium balance is generally the result of renal excretion.

3.1. Systemic Transport of Magnesium

3.1.1. Intestinalt Ransport

The majority of magnesium absorption occurs in the ileum with lesser amounts in the duodenum, jejunum, and colon *(5)*. There appears to be both by saturable transcellular and nonsaturable paracellular transport but the saturable component normally contributes a small portion of total absorption. Nonsaturable paracellular absorption is by passive ionic diffusion and "solvent drag" with water absorption and is most prominent at higher intestinal concentrations of magnesium. At lower magnesium concentrations,

there is evidence for active magnesium absorption that appears to involve the cation channel TRMP6. Abnormalities of this transporter appear to be responsible for the condition hypomagnesemia with secondary hypocalcemia (HSH). Unlike calcium absorption, the role for $1,25(OH)_2$vitamin D regulation of magnesium absorption is controversial. Magnesium does not compete with calcium for absorption but its absorption can be decreased in the presence of substances that bind it like phosphorus.

3.1.2. RENAL HANDLING OF MAGNESIUM

Urinary excretion of magnesium is the product of filtration and renal tubular reabsorption with little evidence for secretion *(4*, *6*, *7)*. Magnesium balance is maintained by changes in tubular reabsorption, which is remarkable being that there is no system regulation as with PTH for calcium. About 80% of total serum magnesium is ultrafilterable which in adults means that about 2000 mg of magnesium are filtered and about 100 mg or 1–3% of the filtered load is excreted in the urine daily. The amount of excreted magnesium can vary from less than 0.5% with magnesium deficiency to up to 80% of the filtered load during magnesium infusion in renal failure.

The proximal renal tubule only reabsorbs 10–15% of the filtered load in adults but 70% in neonates suggesting a change in the permeability to magnesium during development. This increased permeability in neonates may be a passive paracellular pathway not present in adults. Thus the reabsorption of magnesium is very different in mature subjects from calcium in which 60–70% is reabsorbed proximally. In contrast to the proximal tubule, the descending loop of Henle can reabsorb significant amounts of magnesium. The thick ascending limb (TAL) though is responsible for about 70% of magnesium reabsorption with the cortical TAL reabsorbing the major portion. Magnesium reabsorption is driven by the lumen positive transepithelial voltage generated by potassium recycling in this segment. This recycling requires the entry of Na, K, and chloride into the cell by the Na–K–2Cl transporter, exit of K back in to the lumen by ROMK and basolateral exit of Na by Na–K-ATPase and Cl by the chloride channels ClC-K_a and ClC-K_b, both of which require a β-subunit called barttin. The permeability of the paracellular pathway for magnesium and calcium reabsorption has been shown to be controlled by the protein paracellin-1 that is the product of the gene *CLDN16*. There is some evidence for active transcellular reabsorption in the TAL but it is controversial. In the TAL and the distal tubule is found the calcium sensing receptor CaSR, which is responsible for control of magnesium reabsorption (Section 3.2).

The distal tubule is the last segment of the renal tubule demonstrated to reabsorb magnesium and it is responsible for about 10% of the magnesium reabsorption, which is predominantly transcellular and active. Magnesium, driven by the transmembrane negative electrical potential, enters the cell through the divalent ion channel TRPM6. TRPM6 is also found in the intestine and mutations of TRPM6 result in low magnesium GI absorption and renal reabsorption in the condition HSH.

3.2. Regulation of Magnesium Metabolism

Control of magnesium metabolism is predominantly by modulation of renal tubular reabsorption since the intestinal absorption is proportional to intake *(7*, *8)*. Multiple

Table 1
Regulation of Magnesium in Renal Tubule

Agent or condition	*Thick ascending limb*	*Distal tubule*
Parathyroid hormone	Increase	Increase
Calcitonin	Increase	Increase
Vasopressin	Increase	Increase
$1,25(OH)_2$vitamin D	Unknown	Increase
Aldosterone	Increase	Increase
Insulin	Increase	Increase
Hypomagnesemia	Increase	Increase
Hypermagnesemia	Decrease	Decrease
Hypercalcemia	Decrease	Decrease
Volume expansion	Decrease	Decrease
Potassium depletion	Decrease	Decrease
Hypophosphatemia	Decrease	Decrease
Metabolic acidosis	Decrease	Decrease
Metabolic alkalosis	Increase	Increase
Loop diuretics	Decrease	No effect
Thiazide diuretics	No effect	Increase
Amiloride	No effect	Increase

hormones, metabolic conditions and diuretics influence magnesium reabsorption in the TAL and distal tubule (Table 1) but in contrast to calcium, there is no one system dedicated to the regulation of serum magnesium. In the TAL limb, magnesium reabsorption is modulated by changes in the transepithelial voltage, Na–K–2Cl transporter, potassium recycling and paracellin-1 regulation of the paracellular permeability and the agents and conditions that modify magnesium work through these mechanisms. One of the most important regulators of magnesium and calcium reabsorption in both the TAL and distal tubule is the divalent sensing receptor CaSR that is present in many tissues but most importantly the parathyroid and renal tubule. The CaSR responds to changes in plasma magnesium and calcium with a decrease in the paracellular transport of these two divalent cations possibly by affecting paracellin-1. This may be the predominant mechanism by which hypomagnesemia stimulates its renal conservation.

The distal tubule is responsible for determining the final amount of magnesium excreted. It increases magnesium reabsorption not only in response to PTH, calcitonin, and vasopressin but also in response to $1,25(OH)_2$vitamin D. The systemic effect of $1,25(OH)_2$vitamin D administration though may be increased magnesium excretion because of the effect of $1,25(OH)_2$vitamin D on GI absorption and serum calcium and magnesium levels through which CaSR decreases magnesium reabsorption. Other metabolic conditions such as acidosis and intravascular volume status also affect magnesium excretion. Finally, certain diuretics have an important effect on renal tubular magnesium handling. Loop diuretics, which inhibit Na–K–2Cl transporter, acutely decrease magnesium reabsorption in the TAL but its chronic effects are lessened due to enhanced

reabsorption in other parts of the nephron, especially the distal tubule. Thiazide diuretics, which inhibit the Na^+–Cl^- cotransporter, increase magnesium excretion but this may be in part due to associated hypokalemia when given on a chronic basis. In contrast, the potassium sparing diuretic amiloride is also magnesium sparing.

4. NEONATAL MAGNESIUM METABOLISM

Magnesium is transported across the placenta to the fetus with daily accumulation of approximately 5 mg/day *(9)*. Unlike calcium in which the transport appears greatest in the third trimester, placental magnesium transport appears greatest in the first trimester. The transport mechanism is distinct from the one that transports calcium and maintains a fetal magnesium concentration that is greater than the maternal concentration. The magnesium transport is affected by maternal stores so that infants born to mothers who are magnesium depleted will be born with abnormally low stores as well. After birth, intestinal magnesium absorption appears to be greater than that demonstrated later in childhood. There also appears to be greater tubular reabsorption of magnesium by the kidney which in part may be due to increased permeability in the proximal tubule as described in Section 3.1.2. Fractional excretion of magnesium ($FE_{mg} = (U_{mg} \div S_{mg})/U_{cr} \div S_{cr}) \times 100$) less than 1% has been described as compared to excretion in older children and adults of 1–3%. These processes likely contribute to the higher serum magnesium concentrations described in premature infants, especially those less than 35 weeks gestation. The suggested intake for magnesium is 4–15 mg/100 kcal in term infants and 7–17 mg/dL in preterm infants.

5. MEASUREMENT OF MAGNESIUM

Evaluation of magnesium metabolism for the most part is concerned with the determination of the status of magnesium stores to evaluate for evidence of depletion or excess. Since no hormone system is responsible for control of magnesium as is true for calcium with parathyroid hormone and vitamin D, study of such a system is unnecessary.

5.1. Serum Magnesium

Serum magnesium shares several features with serum calcium; first, total magnesium is comprised of three fractions ionized, protein-bound and complexed, secondly, the ionized fraction is physiologically and clinically the most important, and finally, protein binding by magnesium is mostly to albumin and is pH dependent *(10)*. In contrast to calcium, total serum magnesium is not as dependent on the levels of serum albumin since only 20–30% of total magnesium is protein-bound. Therefore, direct measurement of ionized magnesium is usually not available in the clinical setting even though magnesium-specific electrodes have been developed and normal ionized magnesium levels in the serum are 0.44–0.59 mmol/L. The total serum magnesium may be "corrected" for the level of magnesium with the formula: ($Mg_c = Mg_T + (4 - Salb)$) where Mg_c is the "corrected" magnesium, Mg_T is the total magnesium in mmol/L, and Salb is the albumin concentration in g/dL, but generally in clinical practice such "correction" is not performed.

Total serum magnesium is measured by a spectrophotometric method using calmagite as the indicator. Total magnesium is usually measured in serum but heparinized plasma can be used if caution is exercised to avoid certain heparins such as lithium heparin known to artifactually increase plasma magnesium. Citrate and EDTA that can complex magnesium and lower measured levels should never be used. Serum and plasma must be quickly separated from RBCs while avoiding hemolysis to avoid leakage of magnesium out of the cells. For the most part, the serum magnesium status is evaluated by total magnesium with the normal range being 1.6–2.4 mg/dL (1.4–2 mEq/L or 0.7–1.0 mmol/L).

5.2. Evaluation of Body Tissue Stores

Clinical investigators for years have studied methods to evaluate the state of magnesium stores by measuring magnesium levels in bone, erythrocytes, and other tissues *(1*, *3)*. Erythrocyte magnesium correlates poorly with whole body magnesium and is not clinically useful. For the most part serum magnesium is used to estimate bone and total body magnesium but there are times where hypomagnesemia may be present without magnesium depletion. To further investigate the possibility of magnesium depletion, the so-called Magnesium Tolerance Test (MTT) has been described for adults *(11)*. It is based on the principle that in the presence of magnesium depletion, an administered magnesium load will be taken up by bone and other tissue and not be excreted in the urine. The protocol is described in Table 2. The test has not been standardized in children but there is no reason to think that the results would be significantly different in older children than adults. The one caveat is that with abnormal renal magnesium wasting, the test cannot be used.

Table 2
Magnesium Tolerance Test Protocol

1.	Collect 24 h urine for baseline magnesium/creatinine ratio.
2.	Infuse 0.2 mEq (2.4 mg) elemental magnesium per kilogram lean body weight in 50 ml D5W over 4 h.
3.	Collect 24 h urine for magnesium/creatinine starting with the beginning of the infusion,
4.	Calculate percentage magnesium retained with the formula: %Mg retained = 1 – [Postinfusion 24 h urine Mg – Preinfusion urine Mg/creatinine × postinfusion creatinine – total elemental Mg infused × 100]
5.	Definition of magnesium deficiency: >50% retention at 24 h = definite deficiency >25% retention at 24 h = probable deficiency

6. CLINICAL EVALUATION MAGNESIUM RENAL HANDLING

Magnesium balance is maintained by either intestinal absorption or renal excretion. Renal excretion of magnesium usually matches the intestinal absorption and in the presence of magnesium depletion the renal excretion of magnesium should be quite low

(2, 4). In adults it has been shown to be 12 mg/day or less with severe depletion. To test whether there is appropriate renal conservation of magnesium or if the kidney is contributing to the condition by inappropriate magnesium loss into the urine, fractional excretion of magnesium (Fe_{Mg}) can be measured in a spot urine using the formula:

$$FEMg = UMg \times PCr/0.7 \times PMg \times UCr \times 100$$

in which Cr = creatinine, P = plasma, and U = urine.

In non-renal disorders causing hypomagnesemia, the FEMg should be <2% but in renal wasting of magnesium it is typically >5% and is often 15% or greater.

7. GENETIC TESTING OF MAGNESIUM DISORDERS

The genetic cause of many of the hypomagnesemic disorders (Table 5) have been identified and can be measured clinically. At the time of the writing of this chapter, there are CLIA approved laboratories for a number of the described genetic defects. Information for the laboratories can be accessed through GeneTests©, University of Washington, Seattle, WA; www.geneclinics.org, which is funded by the National Library of Medicine, NIH and the National Human Genome Research Institute, NIH. This site provides current information about the different disorders, labs providing testing, what tests are offered, methods used, CLIA status, and contact information.

8. HYPOMAGNESEMIA – INTRODUCTION

Magnesium depletion is a very common and important condition whose severity is often underestimated by the level of serum magnesium. It is almost always the result of decreased gastrointestinal absorption or increased renal loss. Hypomagnesemia can be from rare inherited disorders or be associated with many common GI disorders and medications. Nutritional deficiency of magnesium is also an important contributing factor. The signs and symptoms of hypomagnesemia are usually the result of neuromuscular hyperexcitability or cardiac disturbances. Hypomagnesemia is also an important cause of refractory electrolyte disturbances of calcium and potassium homeostasis.

HYPOMAGNESEMIA CASE SCENARIOS

Case Scenario #1: Multiple electrolyte abnormalities in 12-year-old. You are called to see 12-year-old male who was admitted 2 days prior with diarrhea and weakness. Labs show Na-132 mEq/L, K-2.8 mEq/L, Cl-98 mEq/L, HCO_3-18 mEq/L, calcium-6.8 mg/dL, and albumin 2.8 g/dL. He has been on IV fluids with 40 mEq/L potassium and oral calcium supplements but his labs have not improved. He has a PMH of prematurity with necrotizing enterocolitis, short-gut syndrome, and chronic diarrhea. You perform a physical and he has short stature, and has a positive Trousseau's and Chvostek's signs. You ask the lab to add a magnesium level to the morning labs and the result comes back 0.85 mg/dL.

What is the likely cause of the hypomagnesemia? How does it relate to the other electrolyte disturbances? How would you treat this patient?

Case Scenario #2: Two-day-old neonate with seizures. Full term AGA infant who is a product of a term pregnancy and born by a spontaneous vaginal delivery without complications develops poor feedings followed by a generalized seizure at 48 h of age. Stat labs show normal electrolytes and total serum calcium 5.8 mg/dL and an IV dose of calcium is given without correction of the hypocalcemia. Review of the record shows that the mother has diabetes.

What is the most likely cause and how would you make the diagnosis? What are the emergency steps in the treatment?

9. DEFINITION OF HYPOMAGNESEMIA AND MAGNESIUM DEPLETION

Hypomagnesemia may be defined as serum magnesium levels less than 1.6 mg/dL (1.4 mEq/L or 0.7 mmol/L) *(10)*. Due to lesser protein binding, "pseudohypomagnesemia" due to hypoalbuminemia is not the problem that "pseudohypocalcemia" is with low serum albumin. Whereas hypomagnesemia is relatively easy to define, the characterization of whole body magnesium stores is much more difficult and is discussed in Section 5.2. The evaluation of urinary excretion of a magnesium load with the so-called Magnesium Tolerance Test has been accepted in adults as the best measurement of tissue stores but it has not been well studied in children.

10. CLINICAL FEATURES OF HYPOMAGNESEMIA

The clinical manifestations of hypomagnesemia can be separated into its neuromuscular and cardiac effects and disturbances on calcium and potassium homeostasis (Table 3) *(2, 12)*. The exact role of magnesium depletion on the heart and nervous system is often difficult to separate from concomitant hypocalcemia, hypokalemia, or associated clinical conditions. Conversely, magnesium deficiency must be considered in patients with hypocalcemia, hypokalemia, and any of the signs and symptoms outlined below.

10.1. Neuromuscular Effects

The earliest sign of hypomagnesemia may be neuromuscular irritability, which can be manifested by a positive Trousseau's and Chvostek's signs as described with hypocalcemia *(13)*. Trousseau's sign is elicited by pumping a sphygmomanometer cuff 20 mmHg above the systolic BP for 5 min to produce ischemia of the ulnar nerve. A positive sign is when the metacarpophalangeal joints flex, interphalangeal joints extend, and the thumb adducts. Chvostek's sign is elicited by tapping with three fingers over the facial nerve anterior to the ear. A positive sign can be arranged from twitching of the lip at the angle of the mouth to twitching of nasolabial fold, lateral angle of the eye or finally all of the facial muscles on that side. Although isolated magnesium depletion has been shown to cause neuromuscular irritability, many or most children with positive Trousseau's and Chvostek's signs will have concurrent hypocalcemia.

Table 3
Clinical Manifestations of Hypomagnesemia

Neuromuscular
Positive Trousseau's and Chvostek's signs
Muscle tremor
Muscle weakness
Vertical nystagmus
Seizures
Cardiac
EKG changes
Prolonged PR and QT intervals
Arrhythmias
Supraventricular
Ventricular
Sudden death
Enhancement of digoxin toxicity
Hypertension
Electrolyte
Hypokalemia
Hypocalcemia

Central nervous systems symptoms include seizures that may be tonic–clonic, multifocal motor or generalized. Other symptoms described with hypomagnesemia include vertigo, ataxia, choreo-athetoid movements, and psychiatric changes. A rare but fairly specific sign for hypomagnesemia is vertical nystagmus that may not resolve immediately after correction of hypomagnesemia.

10.2. Cardiac Effects

The cardiac manifestations involve mainly conduction disturbances but in adults there is great interest in the role of magnesium in myocardial infarction *(2)*. The pathophysiology of the abnormality involves the role of magnesium, calcium and potassium on depolarization and repolarization of the myocardium. Electrocardiogram disturbances include prolongation of the PR and QT intervals and widening of the QRS complex. Abnormal T and U waves may develop as well as the electrolyte disturbances become more severe. Mild hypomagnesemia is not associated with arrhythmias but adults with severe hypomagnesemia have developed atrial and most importantly ventricular arrhythmias. Digoxin toxicity is an important condition that can be exacerbated in the presence of hypomagnesemia and hypokalemia.

10.3. Electrolyte Disturbances

Patients with hypomagnesemia often also present with hypocalcemia and hypokalemia *(3)*. Several features of these two disturbances with hypomagnesemia are refractory to treatment unless the underlying magnesium deficiency is corrected. Hypocalcemia and hypokalemia likely play a large role in the symptoms associated

with hypomagnesemia and there are numerous inherited and acquired causes of hypomagnesemia, which also cause wasting of potassium and calcium.

Hypokalemia and potassium depletion has long been recognized as a feature of magnesium depletion. The cause and effect or "chicken and egg" question of which comes first is difficult to discern with hypokalemia and hypomagnesemia. There is both loss of intracellular potassium and renal wasting of potassium in the presence of hypomagnesemia. The pathophysiology may relate to effects of magnesium on intracellular mechanisms involving ATP as well as the functioning of potassium channels. Nevertheless, in patients with refractory hypokalemia, concomitant hypomagnesemia should be sought and treated.

Severe refractory hypocalcemia has long been recognized in pediatrics to be associated with hypomagnesemia. This is not seen with mild hypomagnesemia when magnesium stimulates the CaSR on parathyroid cells similar to calcium but typically is seen with severe hypomagnesemia when the serum magnesium is less than 1.1 mg/dL *(4)*. The mechanism may be due to inhibition of PTH secretion secondary to interference in the generation of second messengers by adenylate cyclase and phospholipase C in part by enhancing the inhibitory action of the CaSR on PTH secretion. There is also a resistance to the action of PTH with magnesium depletion at the level of bone and the kidney so even in the presence of PTH; there is a subnormal tissue effect. The result is refractory hypocalcemia resistant to even IV calcium and 1,25-$(OH)_2$vitamin D unless magnesium is administered concurrently. In patients with severe hypocalcemia and hypomagnesemia who are given magnesium, the PTH secretory response and rise in calcium can occur in minutes but the peripheral response to PTH may take days to fully correct.

11. CAUSES OF HYPOMAGNESEMIA

11.1. Decreased Intake

Hypomagnesemia can be seen with a variety of illnesses associated with decreased intake (Table 4). In these states the renal excretion will decrease to less than 12 mg per day but continued unregulated stool losses from GI secretions result in net negative balance *(1, 14)*. This can result from starvation or unusual diets or with protein-calorie malnutrition. Children with protein-calorie malnutrition may have diarrhea and other factors that contribute to the hypomagnesemia. Also hospitalized patients, especially those in ICU settings on prolonged parenteral therapy are at high risk for magnesium depletion.

11.2. Decreased GI Absorption

A large number of GI illnesses that are associated with chronic diarrhea even without malabsorption can have hypomagnesemia due to the high concentration of magnesium in diarrheal fluid *(11, 14)*. Intestinal malabsorption in conditions such as celiac disease can develop magnesium depletion as result of magnesium binding to free fatty acids to form soaps. The hypomagnesemia can be correlated with the rate of excretion of fecal fat and can be lessened with the institution of a low fat diet. Hypomagnesemia with

Table 4
Causes of Hypomagnesemia

Decreased dietary intake
Starvation
Protein–calorie malnutrition
Total parenteral nutrition
Decreased intestinal absorption
Chronic diarrhea
Malabsorption syndromes – celiac, short gut
Steatorrhea
Hypomagnesemia with secondary hypocalcemia
Increased renal tubular disorders
Gitelman and some Bartter syndrome
Autosomal dominant hypoparathyroidism, Bartter-like phenotype
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
Isolated dominant and recessive hypomagnesemia
Mitochondrial hypomagnesemia
Secondary renal magnesium wasting
Diabetes, DKA
Post-obstructive and post-ATN diuresis
Volume expansion, hyperaldosteronism
Medications
Diuretics, except potassium sparing diuretics
Cisplatin
Amphotericin
Cyclosporin, Tacrolimus
Amphotericin
Other
Pancreatitis
Hyperthyroidism
Burns

secondary hypocalcemia is a rare genetic disorder of the TRPM6 gene on chromosome 9q22 resulting severe hypomagnesemia presenting in infancy with refractory seizures *(15)*. Hypocalcemia unresponsive to calcium replacement results from suppression of PTH secretion (Section 10.3) but which can respond to parenteral or sometimes high-dose enteral magnesium.

11.3. Renal Magnesium Wasting

11.3.1. Functional Magnesium Wasting

There are a variety of disorders in which there is renal wasting of magnesium due to the inhibition of tubular reabsorption of magnesium as described in Section 3.1.2 *(8)*. The first group of disorders are associated with polyuria and can be associated with an osmotic diuresis as is seen with diabetic ketoacidosis or when there is abnormal salt and

water reabsorption as seen in the recovery phase of acute tubular necrosis or during the diuretic phase after relief of urinary obstruction. Renal magnesium wasting is also seen when salt and water reabsorption are inhibited after volume expansion with saline or as a result of hyperaldosteronism. Finally there can be magnesium losses in the urine with tubular dysfunction from interstitial nephritis or after renal transplantation.

11.3.2. Medications

A number of medications cause hypomagnesemia including the loop diuretics and the thiazides, which inhibit salt and water reabsorption and hence the forces driving magnesium reabsorption in the thick ascending limb (TAL) and distal convoluted tubule (DCT), respectively *(8)*. Osmotic diuretics induced by mannitol or with hyperglycemia and glucosuria can also cause magnesuria. Another important cause of renal magnesium wasting is due to tubular toxicity seen with cisplatin, amphotericin B, aminoglycosides, and cyclosporin A. The mechanism and clinical course of each is unique. The magnesium wasting with cisplatin is associated with hypocalciuria suggesting involvement of the DCT and can last for months after the discontinuation of the drug. Amphotericin B induced magnesuria is related to the total cumulative dose and is also associated with hypocalciuria but has the other classic features of renal potassium wasting and distal renal tubular acidosis. Aminoglycosides renal toxicity can present with hypomagnesemia, hypokalemia, hypocalcemia, and tetany and has been associated with high doses. More commonly, mild hypomagnesemia is seen during therapy but reverses shortly after its discontinuation. Finally, the hypomagnesemia of cyclosporine A is common with its use in transplant patients but does not correlate with serum cyclosporine levels or other signs of renal toxicity.

11.3.3. Inherited Renal Magnesium Wasting Disorders

Recent developments in molecular biology have allowed the identification of several inherited disorders of renal wasting and better understanding of the mechanisms of normal and abnormal renal magnesium transport (Table 5) *(8, 15)*. Disorders of salt and water transport in the TAL and DCT are primarily responsible for renal magnesium wasting. Hypomagnesemia has been long recognized as a feature in many patients with Bartter syndrome. We have a much better understanding of the biologic nature of this group of illnesses, which we now subdivide based on the molecular defect and specific features. Whereas most patients who present with the so-called antenatal Bartter syndrome (aBS), which is a disorder of the NKCC2 cotransporter or the ROMK potassium channel do not have significant hypomagnesemia, those with antenatal Bartter syndrome and sensorineural deafness (BSND) can have magnesium levels of 1.2 mg/dL or less. The defective gene product has been creatively named “barttin” and is the B subunit activating the renal chloride channels CLC-Ka and CLC-Kb. This abnormality, which inhibits salt and water reabsorption in both the TAL and DCT, explains the magnesium wasting. These patients can be distinguished from those with aBS by the absence of hypercalciuria and nephrocalcinosis as well as the presence of the deafness. They often require parenteral fluid replacement and can advance to end-stage renal disease.

Table 5
Inherited Causes of Hypomagnesemia with OMIM Numbers

Disease	*OMIM®*	*Gene*	*Protein*
Hypomagnesemia with secondary hypocalcemia	602014	TRPM6	TRPM6
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	603959	CLDN16	Paracellin-1
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular	610036	CLD19	Claudin 19
Autosomal dominant hypomagnesemia with hypocalciuria	154020	FXYD2	γ Subunit Na^+–K^+–ATPase
Activating mutations of divalent ion sensing receptor	601199	CASR	Ca^{2+}/Mg^{2+}-sensing receptor
Gitelman syndrome	263800	SLC12A3	NCCT
Antenatal Bartter syndrome type I	601678	SLC12A1	NKCC2
Antenatal Bartter syndrome type II	241200	KCNJ1	ROMK
Classic Bartter syndrome type III	607364	CLCNKB	CLCKB
Bartter syndrome with sensorineural deafness type IV	602522	BSND or CLCNKA +CLCNKB	Barttin or CLCKA and CLCKB

Adapted from Naderi et al. *(10)*. OMIM is the Online Mendelian Inheritance in Man® (Johns Hopkins University, Baltimore, MD; www.ncbi.nih.gov/sites/entrez?db=OMIM)

Mutations in the *CLCNKB* gene coding for CLC-Kb chloride channel are the cause for classic Bartter syndrome, which is only associated with hypomagnesemia in some of the affected patients. The features of this syndrome are hypokalemic metabolic alkalosis with variable hypercalciuria.

Gitelman syndrome, which is caused by mutations of *SLC12A3*, which codes for the thiazide-sensitive sodium–chloride cotransporter NCCT, is a defect of the DCT and is characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. The cause of magnesium wasting with this defect is not well understood with hypotheses ranging from the abnormal sodium entry into the DCT cells to apoptosis of the early DCT cells, which are responsible for magnesium transport.

Disorders of the divalent ion receptor CaSR, which is expressed in the TAL, cells as well as the parathyroid glands, are also associated with abnormalities in magnesium handling. Autosomal dominant hypoparathyroidism is due to activating mutation of CaSR and patients with this disorder typically have hypomagnesemia in the 1.2–1.4 mg/dL range in addition to hypocalcemia. Treatment with calcium and vitamin D can lead to worsening of the hypercalciuria and hypomagnesemia and should be reserved only for symptomatic hypocalcemia. There is another group of patients with complete activation of CaSR, who have hypomagnesemia due to more severe magnesium wasting and a "Bartter syndrome like" phenotype.

There are several recently described genetic abnormalities of renal magnesium wasting and varying degrees of hypomagnesemia. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a defect of the *CLDN16* gene, which codes for the protein called either claudin-16 or paracellin. Paracellin is essential for the paracellular reabsorption of magnesium in the TAL. These patients present during childhood with the triad of hypomagnesemia, hypercalciuria, and nephrocalcinosis as well as with polyuria, failure to thrive, urinary tract infections, and ocular manifestations including myopia, chorioretinitis, and nystagmus. The hypomagnesemia tends to be severe and so seizures and tetany are common in these patients. Treatment has included magnesium and thiazides to help prevent nephrocalcinosis but the long-term prognosis has been poor with progression to chronic renal failure in early adolescence.

Hypomagnesemia with secondary hypocalcemia (HSH) is a disorder of the *TRPM6* gene that codes for the TRPM6 cation channel. Presenting in the neonatal period, these children can have some of the most severe degrees of hypomagnesemia to the 0.5 mg/dL range resulting in hypoparathyroidism, hypocalcemia, seizures, and tetany. Treatment is with magnesium infusions followed by high-dose oral magnesium with or without parenteral magnesium therapy. Other rare causes of hypomagnesemia are isolated hypomagnesemia of dominant and recessive inheritance. Whereas in the former the gene defect is the *FXYD2* gene, in the latter is not known. Isolated dominant hypomagnesemia is associated with low calcium excretion where as the recessive form usually has normal calcium excretion. Finally, hypomagnesemia has been found to be due to a defect in mitochondrial DNA in a kindred with hypomagnesemia, hypercholesterolemia, and hypertension.

11.4. Hypomagnesemia in Neonates

Hypomagnesemia can present in the neonatal period (Table 6) with hypocalcemia, tremors, and seizures *(16)*. It can often present as a medical emergency with refractory hypocalcemia and seizures that require correction of the hypomagnesemia before other clinical manifestations will respond to treatment. Neonatal hypomagnesemia results from one of the following mechanisms: lack of fetal accumulation due to inadequate placental transport, usually as result of maternal depletion, abnormal gastrointestinal absorption, or renal wasting. The most common etiology presenting within a few days after birth is with infants of diabetic mothers (IDM) where it correlates to the lack of diabetic control and magnesium depletion in the mother but it can also be seen in infants whose mothers have gestational diabetes only. Fetal magnesium depletion can also result from other causes of maternal magnesium depletion and intrauterine growth retardation.

Neonates, especially sick premature infants can suffer from a variety of gastrointestinal disorders resulting in a variety of nutritional deficiencies including hypomagnesemia. Infants with surgery after necrotizing enterocolitis and short gut are at increased risk. In addition to the acquired disorders, hypomagnesemia with secondary hypocalcemia usually presents in infancy (described under Section 11.3.3). Magnesium loss in the urine is a common etiology of mild to severe hypomagnesemia in neonates. Generalized tubular dysfunction is important cause as in older children but the sick neonate

Table 6
Causes of Neonatal Hypomagnesemia

Inadequate placental transport
Maternal insulin dependent diabetes mellitus
Maternal gestational diabetes
Maternal magnesium depletion
Intrauterine growth retardation (IUGR)
Decreased GI absorption
Severe diarrhea or malabsorption
Liver disease
Hypomagnesemia with secondary hypocalcemia
Renal loss
Volume expansion, diuresis
Diuretics – loop diuretics, thiazides
Aminoglycosides
Inherited tubular disorders
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
Isolated dominant or recessive hypomagnesemia
Hypomagnesemia with secondary hyperparathyroidism
Other
Exchange transfusion with citrated blood
Maternal hyperparathyroidism

who is on loop diuretics for lung disease and who have treated with aminoglycosides for infection is a real set-up for clinically significant hypomagnesemia. There are several rare inherited tubular disorders described above in Section 11.3.3 that typically present in infancy.

12. DIAGNOSTIC EVALUATION OF HYPOMAGNESEMIA

The first step in the diagnosis of hypomagnesemia is recognition that a disorder of magnesium may be present in a patient with the signs and symptoms outlined in Table 3 because serum magnesium is not included in any of the popular laboratory "panels." As previously noted, ionized magnesium or "corrected" magnesium values are not needed as with calcium due to the fact that only about 20% of magnesium is protein-bound. A chemistry panel including potassium and calcium should also be measured because of the commonly associated deficiency states of these ions as well as looking for evidence of renal disease or diabetes mellitus. If hypomagnesemia is present, one should review the history and physical for evidence of any of the conditions or treatments listed in Table 4 as a possible cause *(11)*. Renal handling of magnesium should be with the measurement of the fractional excretion of magnesium (Fe_{Mg}) in a spot urine using the formula:

$$FEMg = UMg \times PCr/0.7 \times PMg \times UCr \times 100$$

in which Cr = creatinine; P = plasma; and U = urine. The FEMg should be <2% in the presence of hypomagnesemia and if the FE_{Mg} > 5% then renal wasting should be considered *(2)*. If the renal excretion is very low then nutritional or malabsorptive disorders should sought. Due to the possibility that an important cardiac rhythm disturbance may be present, all patients with moderate to severe hypomagnesemia probably should have an electrocardiogram performed.

13. MANAGEMENT OF HYPOMAGNESEMIA

There are several important principals in the treatment of hypomagnesemia. First, severe hypomagnesemia may be life threatening with hypocalcemia, seizures, and tetany and the serum must be brought up to greater than 1 mg/dL with intravenous replacement over a 5–10 min period *(2*, *11*, *16)*. Secondly, the total body magnesium deficit may not be reflected by the serum magnesium level, especially after treatment and may need prolonged therapy for complete replacement. Thirdly, as serum magnesium rises with intravenous therapy there is significant ongoing renal loss that requires additional therapy. In contrast, if there is renal insufficiency present, magnesium replacement must proceed with caution. Finally, simultaneous deficits of potassium may be present and should be replaced as well. During intravenous therapy monitoring of the deep tendon reflexes may allow detection of hypermagnesemia with levels greater than 2.5 mg/dL.

For severe hypomagnesemia the following doses have been recommended:

1. Neonates. Give 0.1–0.2 ml/kg per dose of 50% magnesium sulfate (0.4–0.8 mEq/kg or 50–100 mg/kg) IV slowly under constant cardiac monitoring, can repeat every 12–24 h.
2. Older children. Give 0.12 ml/kg per dose of 50% magnesium sulfate (0.5 mEq/kg or 60 mg/kg) IV over 1–4 h, can repeat every 12 h.
3. Large adolescents and adults. Give 16–24 ml of 50% magnesium sulfate (64–96 mEq) in 500 ml D5 over 6–8 h, can repeat every 12 h. Use 1/2 dose with renal failure.

For mild hypomagnesemia without significant ongoing loss, avoidance of factors leading to magnesium wasting such as certain diuretics and the addition of magnesium containing foods such as meat, seafood, dairy products, and green vegetables may be sufficient. For moderate hypomagnesemia, oral replacement of magnesium is probably adequate. The dose of elemental magnesium (Table 7) is 10–20 mg/kg/dose up to a maximum of 250–500 mg/dose given 3–4 times per day to avoid the development of diarrhea.

HYPOMAGNESEMIA CASE SCENARIO DISCUSSIONS

Case Scenario #1: This patient has hypocalcemia, hypokalemia, mild hyperchloremic acidosis, and hypomagnesemia. He likely has chronic malabsorption and diarrhea which can contribute to all of the abnormalities but the persistence of the hypocalcemia and hypokalemia suggests that magnesium depletion may be playing a role in the etiology of these disturbances by blocking PTH secretion and action and affecting intracellular K and renal K handling. One could perform a Magnesium Tolerance Test as described

Table 7
Common Oral Formulations of Magnesium

Magnesium salt	*Common brand names (OTC)*	*Elemental Mg*
Magnesium oxide	Mag-Ox® 400 Tablet	242 mg
Magnesium hydroxide	Phillips'® Milk of Magnesia	165 mg/5 ml
Magnesium gluconate	Magonate®	54 mg/5 ml
	Magonate® Tablet	27 mg
Magnesium L-aspartate HCl	Maginex™Granules	122 mg
	Maginex™ Tablet	61 mg
Magnesium chloride	Slow-Mag® Tablet	64 mg

in Section 5.2 to assess whole body magnesium stores but measurement of fractional excretion of magnesium in this hypomagnesemic child will at least give a measure of whether renal conservation is occurring or if the kidney is contributing to the magnesium depletion. The FE_{Mg} described in Section 6 was performed and was 1.8%, which is appropriate in the presence of hypomagnesemia. Other studies to be considered include an ionized calcium to better assess the hypocalcemia as well as a PTH and 25(OH)D levels, which may be causing the low serum calcium. Correction of the hypomagnesemia is likely necessary to allow correction of the hypokalemia and hypocalcemia and you order two doses of 0.12 ml/kg per dose of 50% magnesium sulfate (0.5 mEq/kg or 60 mg/kg) IV each given over 2 h and 12 h apart. The next, the serum potassium is up to 3.8 mEq/L and the calcium is now 9.2 mg/dL with ionized calcium normal at 1.1 mM demonstration the causative nature of the hypomagnesemia on the associated electrolyte disorders. Long-term correction of the total body magnesium depletion with oral magnesium supplements will be required.

Case Scenario #2: Two-day-old neonate with seizures. This infant presents with early neonatal hypocalcemia. There is no history of asphyxia but the infant is an IDM, which is one of the common causes of early neonatal hypocalcemia. Hypomagnesemia is common in IDM due to renal magnesium wasting in the mothers, even with gestational diabetes. It is important to recognize and treat the hypomagnesemia because the hypocalcemia will prove refractory to treatment until the serum magnesium is corrected. You send off blood for serum magnesium and it comes back 0.85 mg/dL. With serum magnesium levels less than 1.0–1.1 mg/dL, there is both inhibition of PTH secretion and its effects on peripheral tissues. With restoration of the serum magnesium levels to above 1.1 mg/dL, this can be rapidly corrected. You give 0.1–0.2 ml/kg per dose of 50% magnesium sulfate (0.4–0.8 mEq/kg or 50–100 mg/kg) IV over 15 min with constant cardiac monitoring or by IM injection. After administration of magnesium the level of calcium and magnesium is monitored and further correction given as needed. There is often a need to repeat the IV magnesium dose after 12–24 h. There may be an underlying abnormality in magnesium metabolism (Sections 11.2 and 11.3, above) but these usually present later than Day 2 of life and will require more long-term and aggressive magnesium therapy.

14. HYPERMAGNESEMIA – INTRODUCTION

Due to the ability of the kidney to excrete a load of magnesium as serum magnesium exceeds the normal range, clinically significant hypermagnesemia is an uncommon disorder in the presence of normal renal function. Hypermagnesemia is almost always the result of either decreased renal function or an increased enteral or parenteral magnesium load. Newborns whose mothers have received parenteral magnesium for preeclampsia are susceptible for hypermagnesemia in part due to their developmentally low glomerular filtration rate.

HYPERMAGNESMIA CASE SCENARIOS

Case Scenario #1: Lethargy in a child in long-term care facility. Five-year-old child with multiple congenital abnormalities is admitted from a long-term care facility with lethargy and hypotension. He has a long history of constipation, which had been treated with resultant diarrhea. His low blood pressure is thought to be due to dehydration as a result of the diarrhea. Fleets enemas were being avoided because of his known chronic renal insufficiency from hypoplastic kidneys as part of an unknown syndrome.

What studies do you want to order? What is the most likely treatment?

Case Scenario #2: Newborn with suspected sepsis. One-day-old term infant noted to be lethargic in the delivery suite develops worsening respiratory depression after treatment with ampicillin and gentamicin are initiated for suspected sepsis. There were no premature rupture of membranes or other risk factors for sepsis.

What other information do you need to assess the cause of the respiratory depression? What lab studies are needed? What is the prognosis?

15. DEFINITION

Serum magnesium levels in the excess of 2.4 mg/dL or (2.0 mEq/L or 1 mmol/L) is considered elevated *(10)* but hypermagnesemia in neonates has been defined as levels in excess of 2.8 mg/dL (2.3 mEq/L or 1.15 mmol/L) *(16)*. Mild elevations of serum magnesium are relatively common in hospitalized patients but have little clinical significance. Unlike serum calcium, where the ionized portion is commonly measured in the clinical setting, measurement of ionized magnesium is not generally available. Also in contrast to hypomagnesemia, where serum levels and total body stores may not correlate with depletion, with magnesium intoxication the level of serum magnesium is sufficient to evaluate the severity of the condition.

16. CLINICAL FEATURES

The clinical features of hypermagnesemia are directly related to the level of serum magnesium and typically are not seen until the level exceeds 3–5 mEq/L *(11*, *14)*. The signs and symptoms of hypermagnesemia arise predominantly from its effects on the cardiovascular and nervous symptoms and generally progress from mild to life threatening severity as the level of magnesium rises but the exact levels at which symptoms occur can vary from patient to patient (Table 8) *(12)*. Magnesium causes flushing and

Table 8
Clinical Manifestations of Hypermagnesemia by Severity

Serum magnesium 3–5 mEq/L
Mild reduction in BP
Drowsiness, lethargy
Flusing
Nausea, vomiting
Serum magnesium 5–10 mEq/L
EKG changes
Hypotension
Decreased deep tendon reflexes
Suppressed ventilation
Serum magnesium >10 mEq/L
Coma
Muscle paralysis
Respiratory paralysis
Refractory hypotension
Complete heart block
Cardiac arrest

hypotension through vasodilatation of the vasculature by blocking calcium channels and induction of prostacyclin as well as by inhibition of norepinephrine release. The effects on the heart progress from prolongation of the PR, QRS, and QT intervals to worsening heart block and ultimately asystole in the most severe cases. The effects on the nervous system are the result of inhibition of acetylcholine release. As serum magnesium increases the effects on the musculature can result in weakness and hyporeflexia to complete paralysis and respiratory failure. Nausea and vomiting are likely the result of smooth muscle inhibition. The central nervous system is also affected and can result in drowsiness to coma as the level of magnesium rises.

17. CAUSES OF HYPERMAGNESEMIA

Hypermagnesemia is usually the result of decreased glomerular filtration rate or increased load. Newborns whose mothers are treated with magnesium for preeclampsia are also at high risk and should be evaluated for hypermagnesemia. Other unusual causes of mild hypermagnesemia are listed in Table 9. Patients with familial hypocalciuric hypercalcemia who have inactivating defects of the CaSR often have mild hypermagnesemia which is usually not clinically significant.

17.1. Renal Failure

Due to the ability of the kidney to increase the fraction excretion of magnesium to virtually 100% of the filtered load, hypermagnesemia does not appear in acute or chronic

Table 9
Causes of Hypermagnesemia

Renal failure
Acute renal failure
Chronic renal insufficiency
End-stage renal disease
Magnesium load
Magnesium containing antacids
Magnesium cathartics
Magnesium enemas
Magnesium infusion
Miscellaneous
Familial hypocalciuria hypercalcemia
Hypothyroidism
GH deficiency
Addison's disease
Neonatal hypermagnesemia
Unknown

renal failure until the GFR falls below 20–30% of normal *(2)*. Significant hypermagnesemia is usually the result of a magnesium load in the setting of renal insufficiency. Therefore, patients known to have renal insufficiency or failure should avoid or limit magnesium containing antacids, cathartics, and enemas. Magnesium containing phosphate binders should be used with caution. An unusual cause of hypermagnesemia in hemodialysis patients is the result improperly treated water for dialysate.

17.2. Excess Magnesium Load

In the presence of normal renal function, severe hypermagnesemia is rare with ingestion of magnesium but mild elevations in serum magnesium are common with the use of magnesium for bowel clean out *(1)*. Patients with inflammatory bowel disease, obstruction or with bowel perforation are at greater risk for clinically significant hypermagnesemia. When magnesium is given parenterally, there is an even greater risk for severe hypermagnesemia. Hypermagnesemia has been induced during pregnancy as a standard treatment for preeclampsia and premature labor for many years.

17.3. Neonatal Hypermagnesemia

Hypermagnesemia in neonates is usually the result of magnesium crossing the placenta after magnesium sulfate administration to the mother for treatment of preeclampsia and premature labor *(16)*. Severe hypermagnesemia is unusual and typically resolves in a few days. Other causes of hypermagnesemia in neonates are the administration of magnesium with total parenteral nutrition and with intravenous magnesium sulfate for the treatment of persistent pulmonary hypertension. Studies have shown that total serum magnesium levels are greater in very premature infants as compared to term infants

but that the more physiologically important ultrafilterable fraction of magnesium is not significantly different. The presentation of hypermagnesemia in neonates is that of a depressed infant with hypotonia but in the worst cases it can be severe and lead to respiratory failure due to a curare-like effect. Hypocalcemia may be present as well as result of inhibition of PTH secretion by the high magnesium.

18. DIAGNOSIS OF HYPERMAGNESEMIA

One should suspect the diagnosis of hypermagnesemia when the cardiac and neuromuscular symptoms as outlined in Table 8 are seen in a patient with renal insufficiency or after administration of magnesium with enterally or parenterally. A careful history is important to look for potential causes (Table 9), in particular, the maternal record needs to be reviewed in the management of a depressed newborn. In addition to the measurement of total serum magnesium, renal function, electrolytes, and serum calcium should be measured in the initial lab evaluation. An electrocardiogram should be performed to look for any cardiac electrical disturbances.

19. MANAGEMENT OF HYPERMAGNESEMIA

In the presence of normal renal function the management is largely supportive as one waits for the kidneys to excrete the excess magnesium *(3*, *14)*. Hydration and loop diuretics may augment the renal excretion. In severe hypermagnesemia, some of the manifestations can be acutely reversed by the administration of intravenous calcium. In older children, the dose is 100–200 mg of elemental calcium IV over 5–10 min and in neonates it is calcium gluconate, 100 mg/kg (9 mg/kg elemental calcium) over 20 min. The calcium can be repeated but the levels of total and ionized calcium should be monitored. In the most severe cases or in the setting of renal failure, peritoneal or hemodialysis with a low magnesium bath is able to rapidly correct the hypermagnesemia. In neonates, exchange transfusion with citrated blood has been used in life threatening cases to more effectively lower serum magnesium.

CASE SCENARIO DISCUSSIONS

Case Scenario #1: Lethargy in a child in a long-term care facility. This child with lethargy and hypotension could have many reasons for his signs and symptoms including sepsis. A careful review of events finds that he has been given an excessive amount of magnesium citrate, which resulted in diarrhea and dehydration. A serum magnesium level is added to a chemistry panel and comes back at 7.2 mg/dL and his serum creatinine is 4.2 mg/dL as compared to his baseline of 2.8 mg/dL. The dehydration from the cathartic caused an acute deterioration of his renal function that then contributed to his inability to handle the magnesium load. The treatment is support of his blood pressure with normal saline and the careful use of loop diuretics after rehydration to aide renal excretion of magnesium but not to exacerbate the dehydration is indicated. A bolus of intravenous calcium at a dose of 100 mg of elemental calcium over 10 min may reverse

some of the effects of the hypermagnesemia. If the renal function and hypermagnesemia are severe enough, dialysis may be necessary.

Case Scenario #2: Newborn with suspected sepsis. This infant presents with lethargy and respiratory distress like so many infants but the history revealed that this case differs in that the mother had preeclampsia and had been treated with magnesium. Unfortunately for her and her infant, the dose was excessive and both developed hypermagnesemia. The serum magnesium in the fetus was 6.4 mg/dL, total calcium 8.9 mg/dL, and ionized calcium 0.95 mM. The mild hypocalcemia is the likely result of suppression of PTH secretion by high levels of magnesium. In this case the therapy is supportive with IV calcium gluconate at a dose of 100 mg/kg (9 mg/kg elemental calcium) over 20 min to help reverse the respiratory depression, hydration to help assist urinary excretion and possibly the use of a loop diuretic like furosemide to enhance renal excretion. The electrolyte disturbance should resolve in 48 h with good supportive care.

REFERENCES

1. Agus ZS, Massry SG. Hypomagnesemia and hypermagnesemia. In: Narins RG, ed., Maxwell & Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism, 5th ed., New York: McGraw-Hill, 1994:1099–1119.
2. Reikes S, Gonzalez EA, Martin KJ. Abnormal calcium and magnesium metabolism. In: DuBose TD, Hamm LL, ed., Acid–Base and Electrolyte Disorders. Philadelphia: Saunders, 2002: 453–487.
3. Alfrey AC. Disorders of magnesium metabolism. In: Seldin DW, Giebisch G, eds., The Kidney: Physiology and Pathophysiology, 2nd ed., New York: Raven Press, 1992:2357–2373.
4. Hruska KA, Levi M, Slatopolsky E. Disorders of phosphorus, calcium, magnesium metabolism. In: Schrier RW, ed., Disorders of the Kidney & Urinary Tract, 8th ed., Vol. 3. Philadelphia: Lippincott Williams & Wilkins, 2007:2295–2352.
5. Favus MJ. Intestinal absorption of calcium, magnesium and phosphorus. In: Coe FL, Favus MJ, eds., Disorders of Bone and Mineral Metabolism, 2nd ed., Philadelphia: Lippincott Williams & Wilkins, 2002:34–47.
6. Yu ASL. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, ed., Brenner & Rector's The Kidney, 7th ed., Vol. 1. Philadelphia: Saunders, 2004:535–571.
7. Quamme GA, Cole DEC. Physiology and pathophysiology of renal magnesium handling. In: Coe FL, Favus MJ, eds., Disorders of Bone and Mineral Metabolism, 2nd ed., Philadelphia: Lippincott Williams & Wilkins, 2002:34–47.
8. Quamme GA, Schlingmann KP, Konrad M. Mechanisms and disorders of magnesium metabolism. In: Alpern RJ, Hebert SC, eds., Seldin and Giebisch's The Kidney, 4th ed., Vol. 2. Boston: Elsevier, 2008:1747–1767.
9. Rigo J, De Curtis M. Disorders of calcium, phosphorus, and magnesium metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, eds., Fanaroff and Martin's Neonatal–Perinatal Medicine, 8th ed., Vol. 2. Philadelphia: Mosby, 2006:1491–1520
10. Vokes TJ. Blood calcium, phosphate, and magnesium. In: Favus MJ, ed., Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th ed., Washington DC: American Society of Bone and Mineral Research, 2006:123–127
11. Rude RK. Magnesium depletion and hypermagnesemia. In: Favus MJ, ed., Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th ed., Washington DC: American Society of Bone and Mineral Research, 2006:123–127.
12. Penfield JG, Choudhury D, Cronin RE, Knochel JP, Levi M.. Disorders of Phosphate and Magnesium Metabolism. In: Coe FL, Favus MJ, eds., Disorders of Bone and Mineral Metabolism, 2nd ed., Philadelphia: Lippincott Williams & Wilkins, 2002:589–615.

13. Fitzpatrick LA. The hypocalcemic states. In: Coe FL, Favus MJ, eds., Disorders of Bone and Mineral Metabolism, 2nd ed., Philadelphia: Lippincott Williams & Wilkins, 2002:568–588.
14. Pollack MR, Yu ASL. Clinical disturbances of calcium, magnesium, and phosphate metabolism. In: Brenner BM, ed., Brenner & Rector's The Kidney, 7th ed., Vol. 1. Philadelphia: Saunders, 2004: 535–571.
15. Naderi ASA, Reilly RF. Hereditary etiologies of hypomagnesemia. Nature Clinical Practice Nephrology 2008;4:80–89.
16. Rigo J, De Curtis M. Disorders of calcium, phosphorus, and magnesium metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, eds., Fanaroff and Martin's Neonatal–Perinatal Medicine, 8th ed., Vol. 2. Philadelphia: Mosby, 2006:1491–1520.