Magnesium in critical illness: metabolism, assessment, and treatment

Introduction

Magnesium is the second most abundant intracellular cation and the fourth most common cation in the body [1]. Its importance as an essential nutrient has been recognized since 1932, when Kruse et al. [2] reported the effects of acute Mg deficiency in rats. Even recently Mg was considered the “forgotten cation” in clinical practice [3]; however, this is no longer the case [4]. Estimates of Mg deficiency range from 20% to 61% [5, 6, 7], while a recent study found that reductions in total serum Mg on admission are associated with increased mortality [8].

Nonetheless, the relevance of such data to intensive care is problematic. Controlled data are lacking on how circulating total Mg concentrations are related to levels of biologically active ionized Mg (Mg²⁺). Data are likewise sparse concerning the interplay between serum total and ionized Mg levels during specific critical illnesses and their treatment. In particular, the efficacy of therapeutic Mg supplementation on Mg²⁺, organ function, inflammatory events, and mortality are poorly understood. This lack of information on the biology of Mg contrasts with well established correlations between serum total and ionized calcium (Ca²⁺) concentrations, manifestations of acute Ca²⁺ deficiency, and the physiological effects of correcting ionized hypocalcemia [9, 10, 11, 12].

This review summarizes key aspects of Mg metabolism in adult intensive care patients, emphasizing the interdependence of Mg homeostasis with that of other cations such as Ca²⁺ and K⁺. Thereafter we examine the justification for the trend of increasingly frequent measurements of serum total Mg in the critically ill, and how this information is related to emerging data concerning circulating Mg²⁺. In this context, the limitations of current treatment recommendations for hypomagnesemia in the ICU are analyzed as well as research developments likely to alter our diagnostic and therapeutic algorithms in the near future. The use of therapeutic doses of Mg independent of hypomagnesemia or titration to serum total Mg levels to treat conditions such as preeclampsia and asthma are covered since this is beyond the scope of this review.

Compartmental distribution and metabolism of Mg

The body normally contains 21–28 g Mg [13]. Approximately 53% of total Mg stores are in bone, 27% in muscle, 19% in soft tissues, 0.5% in erythrocytes, and 0.3% in serum [14]. The Mg in muscle, soft tissues, and erythrocytes is considered to be intracellular [1], and mostly bound to chelators such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), proteins, RNA, DNA, and citrate [14]. Although only 5–10% of intracellular Mg is ionized, this fraction is essential for regulating intracellular Mg homeostasis [15] (Fig. 1).

Traditionally, extracellular Mg in serum was considered to be 33% protein bound, 7% complexed to citrate, PO₄²⁻, and HCO₃⁻ [16], and 55% circulating in the diva-
lent ionized form (Mg\(^{2+}\)). However, the newer methods of ion-selective Mg electrodes, atomic absorption spectroscopy, and ultrafiltration indicate that serum Mg is 67% ionized, 19% protein bound, and 14% complexed [17]. Standard clinical determinations of serum total Mg reflect all three forms. Of note, protein-bound and complexed Mg are unavailable for most biochemical processes [1]. The important issue of the dynamics of equilibration among the various states of extracellular Mg has not been extensively studied. Since serum contains only 0.3% of total body Mg stores, serum total Mg measurements poorly reflect total body status. Serum total Mg concentrations normally average 1.7–2.3 mg/dl (1.4–2.1 mEq/l) [13], depending on the laboratory and measurement technique. Mg concentrations are commonly expressed in units of milligrams, millimoles, or milliequivalents; for conversion one can use the following formula: 1 g Mg sulfate contains 98 mg = 4.06 mmol = 8.12 mEq elemental Mg.

Daily Mg intake in adults normally averages 6–10 mg/kg [18]. Absorption occurs primarily in the jejunum and ileum [19]. Several lines of evidence suggest that absorption involves a transcellular, saturable process involving facilitated diffusion and a passive intercellular mechanism mediated by cationic electrochemical gradi-
Mg represent buffers whose chief function appears to be maintaining constancy of the intracellular concentration of free \([\text{Mg}^{2+}]\). In human erythrocytes and other cells an increase in \([\text{Mg}^{2+}]\), by Mg loading is associated with Mg efflux via the Na\(^{+}\)/\text{Mg}^{2+} antiport until \([\text{Mg}^{2+}]\), is normalized. Furthermore, reductions in \([\text{Mg}^{2+}]\), stimulate cationic diffusion down a concentration gradient from higher levels of extracellular \(\text{Mg}^{2+}\) [35, 36]. Consequently, Mg homeostasis is regulated chiefly by \([\text{Mg}^{2+}]\), which is in equilibrium with both intracellular bound Mg and extracellular \(\text{Mg}^{2+}\). Neither the magnitude nor the efficiency of these compensatory mechanisms is known for critically ill patients, in whom counterregulatory hormone release, insulin administration, and de novo renal and gastrointestinal dysfunction are common.

**Biochemical, biological, and physiological effects of Mg**

Mg is important in physiological processes involving energy storage, transfer, and utilization [13, 37]. Mg complexed to ATP is a substrate for signal-transducing enzymes including phosphatases and phosphokinases on the plasma membrane and within intracellular compartments. Enzymatic reactions involving ATP require \(\text{Mg}^{2+}\), which neutralizes the negative charge on ATP to facilitate binding to enzymes and assists hydrolysis of the terminal PO\(_4^{2–}\) bond [38]. Intracellular \(\text{Mg}^{2+}\) regulates intermediary metabolism by activating rate-limiting glycolytic and tricarboxylic acid cycle enzymes [39]. \(\text{Mg}^{2+}\)-ATPases include \(\text{Mg}^{2+}-(\text{Na}^+-\text{K}^+)\) ATPase, \(\text{Mg}^{2+}-(\text{HCO}_3^–)\) ATPase, and \(\text{Ca}^{2+}-\text{Mg}^{2+}\) ATPase, which are involved in \(\text{Na}^+, \text{proton, and Ca}^{2+}\) transport, respectively [40]. Mg indirectly affects protein synthesis by four mechanisms: (a) facilitation of nucleic acid polymerization, (b) enhanced binding of ribosomes to mRNA, (c) acceleration of the synthesis and degradation of DNA, and (d) regulation of protein:DNA interactions and thus transcriptional activity [41, 42]. Adenylate cyclase also requires Mg to generate the intracellular second messenger cAMP [40].

Intracellular \(\text{Mg}^{2+}\) significantly affects \(\text{Ca}^{2+}\) and \(\text{K}^+\) metabolism. As a divalent cation \(\text{Mg}^{2+}\) competes with \(\text{Ca}^{2+}\) for membrane-binding sites and modulates \(\text{Ca}^{2+}\) binding and release from the sarcoplasmic reticulum [43]. Complementary effects include maintenance of low resting levels of intracellular \(\text{Ca}^{2+}\), thereby modulating muscle contraction by noncompetitive inhibition of inositol 1,4,5-triphosphate gated \(\text{Ca}^{2+}\) channels [44]. Calcium metabolism is controlled chiefly through PTH; substantial evidence indicates that Mg modulates Ca balance by its actions on PTH itself [45]. For example, impaired PTH secretion associated with hypomagnesemia results in hypocalcemia. This is attributed to reduced Mg-dependent activation of adenylate cyclase in parathyroid tissue [46, 47]. Whether Mg deficiency also contributes to skeletal muscle resistance to PTH is controversial [48].

\(\text{Mg}^{2+}\) regulates K\(^+\) transport via the \(\text{Na}^+-\text{K}^+-\text{ATPase}\) system as a cofactor. This action influences \(\text{Na}^+\) and K\(^+\) extracellular fluxes, which determine the electrical potential across cell membranes [49]. \([\text{Mg}^{2+}]\), blocks outward movement of K\(^+\) through K\(^+\) channels in cardiac cells. Decreases in \([\text{Mg}^{2+}]\), cause excessive outward movement of K\(^+\) even as intracellular K\(^+\) falls, thereby inducing depolarization [50]. This critical role of \(\text{Mg}^{2+}\) to maintain intracellular K\(^+\) concentrations is termed “inward rectification” [51]. \(\text{Mg}^{2+}\) deficiency also impairs K\(^+-\text{Na}^+-\text{Cl}^–\) cotransport [52].

In the nervous system Mg has a depressant effect at the synapses; this is related to competition with calcium in the stimulus-secretion coupling processes in transmitter release. The best described of these is presynaptic inhibition of acetylcholine release at the neuromuscular junction [53]. The action of Mg as an anticonvulsant is related to noncompetitive blockade of N-methyl-D-aspartate receptors. These are a group of glutamate receptors, stimulation of which leads to excitatory postsynaptic potentials causing seizures [54].

Overall, \(\text{Mg}^{2+}\) deficiency has the potential to impair oxidative phosphorylation, protein metabolism, and transmembrane electrolyte flux in cardiac and neural tissues.

**Assessment of Mg status**

Assessing Mg status in the critically ill beyond serum total Mg levels is difficult. No single laboratory test tracks total body Mg stores. In all, three groups of tests are available: (a) estimates of tissue Mg using concentrations in serum, red blood cells, blood mononuclear cells, or muscle; (b) metabolic assessments of Mg balance encompassing isotopic analyses and evaluation of renal Mg excretion and retention, and (c) determination of Mg\(^{2+}\) levels which utilize fluorescent probes, nuclear magnetic resonance spectroscopy, or ion-selective electrodes (ISE).

Measuring total Mg concentrations in serum rather than plasma has been preferred because additives such as anticoagulants may be contaminated with Mg or otherwise affect the assay. For example, citrate binds Ca\(^{2+}\) as well as \(\text{Mg}^{2+}\) to affect fluorometric (8-hydroxyquinoline) and colorimetric procedures for Mg estimation [55]. As indicated above, serum total Mg levels reflect Mg\(^{2+}\), the protein-bound Mg fraction, and Mg complexed to anions, and each component of the total value may change independently and in a nonlinear manner with respect to the other Mg fractions.

Most clinical laboratories report serum total Mg concentrations using colorimetric methods with calmagite or methylthymol blue as the chromophore [56]. As men-
tione above, the chief limitation is that serum concentrations represent only 0.3% of total body Mg content [14]. Moreover, with the exception of bone, serum total Mg concentrations are not correlated with other tissue pools of Mg [57]. As for Ca, normal total Mg levels may coexist with ionized hypomagnesemia and vice versa [58]. Red blood cell Mg determinations have no advantage over serum levels and also are not correlated with other tissue fractions [57]. In normal subjects there is no correlation among Mg levels in mononuclear cells compared with serum or erythrocytes [59]. In a prospective controlled study measuring skeletal muscle Mg concentrations in 32 ICU patients with respiratory failure no correlation was found between serum total and muscle Mg concentrations [60]. Lower muscle Mg levels were associated with reduced intracellular K+ levels, a higher incidence of ventricular extrasystoles, and a longer ICU stay.

Physiological assessments of Mg balance require steady-state conditions for accurate results, conditions that are infrequent in the critically ill. A 24-h urine collection for renal Mg excretion takes into account the circadian rhythm of cationic urinary losses [61]. However, existence of this rhythm during critical illness is unknown. Even so, a 24-h Mg excretion rate of less than 12 mg/day is acceptable evidence of Mg deficiency in the presence of serum total hypomagnesemia and normal renal function [23]. The Mg tolerance test has been used for many years as a fairly reliable means of assessing total body Mg status in patients at risk of hypomagnesemia [62]. Subjects with normal Mg balance and renal function excrete most of a parenterally administered Mg load within 24 h [28, 62]. A generally accepted protocol includes: (a) a baseline 24-h urine collection for Mg, followed immediately by (b) an infusion of 2.4 mg Mg per kilogram of lean body weight in 50 ml 5% dextrose over 4 h, and (c) a second 24-h urine collection. Differences in Mg content between the two urine collections represent the retained Mg fraction. Retention of more than 20% of administered Mg is suggestive of Mg deficiency, whereas retention of more than 50% is confirmatory [40]. This test is contraindicated when serum creatinine exceeds 200 µmol/l. Furthermore, drugs or conditions producing renal Mg wasting invalidate the results. Using the Mg loading test, serum ionized Mg levels were found to be insensitive markers of Mg deficiency in 44 ICU patients without renal insufficiency [63]. However, confounding variables, such as the use of diuretics, prevent any firm conclusions to be drawn.

A major advance in evaluating Mg deficiency is the ability to measure Mg2+. In 1989 Raju et al. [64] modified the calcium fluoroprobe fura-2 to improve selectivity for Mg2+. The resulting compound furaptra (mag fura-2) exhibits a shift in the peak excitation wavelength for fluorescence when bound to Mg2+ or Ca2+. The change in fluorescence corresponds to Mg2+ and Ca2+ concentrations weighted by their respective dissociation constants. For Mg2+, these probes work well within the cell. Other fluorescent probes for Mg2+ have been described [65]. Nuclear magnetic resonance spectroscopy estimates Mg2+ noninvasively. Although several isotopes (19F-, 23Mg2+, and 31P−) have been used to estimate Mg2+, the α- and β-phosphate moieties of ATP have been used most frequently [66].

Three ISEs for Mg2+ determination are currently available: (a) the NOV A 8 analyzer (NOV A, Waltham, Mass., USA); (b) the Microlyte 6 analyzer (Kone, Espoo, Finland); and (c) the AVL 988/4 analyzer (AVL, Schaffhausen, Switzerland). In May 1993 the United States Food and Drug Administration approved the NOV A 8 electrode for clinical use, and most studies of Mg2+ have used the NOV A 8 instrument. These ISEs employ ionophores and neutral carrier-based membranes designed to function in the presence of Ca2+ and other cations. Mg2+-specific ISEs yield rapid results on whole blood, plasma, and serum using samples between 100–200 µl. Ionized Mg concentrations in healthy subjects using the NOV A 8 average 0.54–0.67 mmol/l [58, 67]. Serum reference intervals for the Kone and AVL analyzers are 0.47–0.57 mmol/l and 0.55–0.63 mmol/l, respectively [68]. No gender-related differences in Mg2+ have been described [67]. To date ISEs have been found to be selective for Mg2+; physiological concentrations of Ca2+, Na+, K+, H+ and NH4+ have negligible effects. Therefore the precision of these analyzers is suitable for determining Mg2+ in intensive care [67].

The NOV A 8 and AVL analyzers correct signals from the Mg2+ electrode for concurrent Ca2+. Calculations of Mg2+ and Ca2+ are normalized to a pH of 7.4 in the NOV A 8 instrument, which also estimates Na+, K+, Ca2+, hematocrit, and pH [69]. The binding capacity and affinity of albumin for Mg2+ and Ca2+ varies with pH [70]; hence the Mg2+ and Ca2+ levels are pH dependent. Because of pH changes during specimen storage, measured Mg2+ can be reported as the Mg2+ at the pH of the blood sample (preferably) or as Mg2+ normalized to a pH of 7.4.

**Mg deficiency in intensive care**

Ideally, Welt and Gitelman’s [71] definition of hypomagnesemia as “a reduction in total body magnesium content” defines true Mg deficiency. Unfortunately, this definition of Mg deficiency is not in keeping with commonly available laboratory technology. In spite of its imperfections serum total Mg is still used as the standard for defining hypomagnesemia in intensive care patients.
Clinical manifestations of hypomagnesemia

Most hypomagnesemia in intensive care is asymptomatic. In theory, symptoms and signs occur when the serum total Mg concentrations fall below 1.2 mg/dl (0.5 mmol/l) [72], as summarized below:

- Neuromuscular manifestations
  - Positive Chvostek’s sign
  - Positive Trousseau’s sign
  - Carpopedal spasm (tetany)
  - Muscle cramps
  - Muscle fasciculations and tremor
  - Muscle weakness

- Neurological manifestations
  - Convulsions
  - Nystagmus
  - Athetoid movements
  - Apathy
  - Delirium
  - Coma

- Cardiac manifestations
  - Supraventricular arrhythmias
  - Ventricular arrhythmias
  - Torsades de pointes
  - Enhanced sensitivity to digitalis intoxication

- Electrolyte disturbances
  - Hypokalemia
  - Hypocalcemia

However, manifestations of hypomagnesemia may depend more on the rate of development of the deficiency, on serum ionized rather than total hypomagnesemia, or on tissue Mg deficits rather than on circulating levels [73]. Consequently symptoms and signs ascribed to Mg deficiency may be absent even with severe hypomagnesemia (serum total Mg levels <0.8 mg/dl) [72]. Such dissociations between serum total Mg levels and clinical findings make it difficult to infer total body Mg deficiency, the need for correction of hypomagnesemia, and the physiological benefit of such correction in individual patients.

Neuromuscular manifestations of hypomagnesemia: relationship to hypocalcemia

Serum total hypomagnesemia is usually corrected because of concerns over neuromuscular irritability (e.g., positive Chvostek’s and Trousseau’s signs, tremors, fasciculations, and tetany) or weakness [74]. In particular, the possibility of weakness and resultant delays in ventilatory weaning attributable to hypomagnesemia have resulted in the widespread practice of frequent measurements and vigorous normalization of serum total Mg levels in ventilated patients. However, no controlled data support this practice, and its putative physiological benefit to respiratory muscle function remains obscure. Indeed, neuromuscular manifestations of serum total hypomagnesemia may be due more to concomitant hypocalcemia, even though tetany attributable solely to hypomagnesemia can occur independently of reduced serum total Ca levels [75]. Overall, neuromuscular irritability and weakness appear to be related to the combined actions of ionized hypomagnesemia and ionized hypocalcemia on the neuromuscular apparatus. Hypocalcemia does not usually develop until serum total Mg is below 1.2 mg/dl; serum total hypocalcemia occurs in one-third of hypomagnesemic medical ICU patients [76]. Hypocalcemia is usually refractory to Ca repletion unless Mg is first administered [76, 77].

Neurological manifestations of hypomagnesemia

Reported neurological manifestations of hypomagnesemia include convulsions, athetoid movements, nystagmus, apathy, delirium, and coma [40]. As mentioned above, the anticonvulsant effect of Mg appears to be via a voltage-gated antagonist action at the N-methyl-D-aspartate receptor [54].

Cardiac electrophysiology, hypomagnesemia, and hypokalemia

The frequency and pathogenesis of cardiac arrhythmias during hypomagnesemia [78] are hard to establish because coexisting hypokalemia is common. Whang et al. [79] reported hypokalemia in 42% of hypomagnesemic patients. Such hypokalemia is also refractory to treatment unless Mg is first repleted [74]. Although Mg per se does not participate in the production of the cardiac action potential [80], Watanabe and Dreifus [81] showed that Mg’s effects on cardiac transmembrane potentials varied in perfused rat hearts according to extracellular K+ levels. Increases or decreases in Mg levels with normal extracellular K+ concentrations causes minor electrophysiological changes. Alterations in serum total Mg concentrations are unlikely to destabilize sinus rhythm unless accompanied by changes in other cations [80].

Serum total Mg levels below 0.7 mmol/l are associated with electrocardiographic changes indistinguishable from hypokalemia-related effects, including ST segment depression, flattened T waves, and prolongation of PR and QT/QTc intervals [38]. Arrhythmias associated with serum total hypomagnesemia include premature atrial contractions, atrial fibrillation, multifocal atrial tachycar-
dia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation [82, 83]. Hypomagnesemia promotes digitalis-induced arrhythmias [84]. The mechanisms are unclear but include: (a) increased myocardial uptake of digoxin, (b) augmented inhibitory action of digoxin on Na\(^+\)-K\(^+\)-ATPase causing a reduction in intracellular K\(^+\) [82], and (c) loss of the membrane-stabilizing effect Mg\(^{2+}\) on the myocardial cell membranes [84]. Mg therapy is recommended for torsades de pointes [85]. Despite these associations of low serum total Mg levels with cardiac electrophysiological changes, purported links between low Mg and arrhythmias do not confirm a cause and effect relationship. Lack of a standard by which to define a Mg-deficient state, coexistence of other electrolyte abnormalities, varying methods of arrhythmia monitoring, and inability to distinguish between spontaneous and drug-induced arrhythmia termination are all factors [80]. Moreover, a prospective uncontrolled study of 23 heart failure patients found no correlation between serum total Mg and myocardial Mg concentrations [86].

### Causes of Mg deficiency in intensive care

Singly or combined, Mg deficiency in intensive care has three main causes – (a) reduced intestinal absorption, (b) increased renal losses, and (c) compartmental redistribution, as detailed below.

**Gastrointestinal causes include:**
- Nutritional disturbances
  - Inadequate intake
  - Mg-free fluids and total parenteral nutrition
  - Refeeding syndrome
- Reduced absorption
  - Malabsorption syndromes
  - Short bowel syndrome
  - Chronic diarrhea
- Increased intestinal losses
  - Intestinal and biliary fistulae
  - Prolonged nasogastric suction
- Pancreatitis

**Causes related to renal Mg wasting include:**
- Drug-induced renal Mg wasting
  - Loop and thiazide diuretics
  - Cisplatin
  - Cyclosporine A
  - Aminoglycosides
  - Amphotericin B
  - Pentamidine and foscarnet
  - Colony-stimulating factor therapy
- Hypophosphatemia
- Hypercalcaemia/hypercalciuria

**Endocrine causes include:**
- Hyperaldosteronism
- Hyperparathyroidism
- Hyperthyroidism
- Syndrome of inappropriate antidiuretic hormone
- Diabetic ketoacidosis
- Alcoholic ketoacidosis

**Causes related to the redistribution of Mg include:**
- Acute pancreatitis
- Administration of epinephrine
- “Hungry bone” syndrome
- Massive blood transfusion
- Acute respiratory alkalosis

**Other causes include:**
- Cardiopulmonary bypass
- Severe burns
- Excessive sweating
- Chronic alcoholism and alcoholic withdrawal

Nearly all data concerning hypomagnesemia during critical illness comes from measurements of circulating total Mg. These do not shed light on the causes of Mg deficiency and likely underestimate ionized hypomagnesemia and total body Mg depletion.

**Gastrointestinal causes**

Prolonged administration of Mg-free parenteral nutrition formulae and other intravenous fluids can precipitate Mg deficiency, especially in patients with preexisting marginal stores of Mg [87]. Vomiting and nasogastric suction further contribute to Mg depletion [48], since the Mg content of upper intestinal fluids is about 1 mEq/l. Diarrheal fluids and fistula drainage contain up to 15 mEq/l total Mg ions [88]. Hemorrhagic pancreatitis is an additional cause of acute hypomagnesemia with hypocalcemia due to formation of Mg and Ca fatty acid soaps in sites of tissue necrosis [89].
Renal Mg wasting is traditionally diagnosed when the 24 h urinary Mg excretion exceeds 24 mg in the presence of hypomagnesemia as assessed by serum total Mg levels [91]. Random or “spot” urinary tests for Mg are interesting albeit unvalidated diagnostic tests. Renal Mg wasting has been reported with tubulointerstitial renal diseases, postobstructive diuresis, the diuretic phase of acute tubular necrosis, and following renal transplantation [90]. Since Mg absorption in the thick ascending loop of Henlé depends on the positive transmembrane potential created by NaCl absorption, alterations in NaCl transport by loop diuretics, 0.9% NaCl infusion, or osmotic diuresis promote Mg excretion. Loop diuretics (furosemide, bumetamide, and ethacrynic acid) are potent inhibitors of Mg reabsorption and are a common cause of hypomagnesemia in the ICU. Thiazide diuretics act on the distal tubule, where less than 5% of Mg is absorbed. Short-term administration of thiazides does not produce significant renal Mg wasting, whereas long-term administration may produce substantial Mg deficiency [40].

Several drugs cause excessive renal losses of Mg. Cisplatin causes hypomagnesemia in more than 50% of treated patients [91]; the incidence increases with the cumulative dose. Likewise, aminoglycosides induce magnesiumuria; 4.5% of 200 patients treated with 400 courses of aminoglycosides developed hypomagnesemia [92]. The total dose of aminoglycoside treatment in these studies varied from 1.3–40 g and recovery from hypomagnesemia varied from 2–8 weeks. A recent prospective study showed ionized hypomagnesemia secondary to renal Mg wasting in cystic fibrosis patients treated with a 2-week course of 33 mg/kg amikacin daily and 250 mg/kg ceftriaxone daily [93], although no clinical correlation with ionized hypomagnesemia was performed. Amphotericin B causes mild and reversible hypomagnesemia [94]. Barton et al [94], reported that reversal of amphotericin B-induced renal Mg wasting could take as long as 1 year following treatment. As with amphotericin B, cyclosporine A causes Mg deficiency secondary to defects in renal tubular function [95]. Parenteral pentamidine has also been implicated in hypomagnesemia secondary to renal Mg wasting [96].

Hypophosphatemia is common during intensive care, particularly in insulin-dependent diabetics and during Gram-negative bacterial sepsis [97]. Although hypophosphatemia promotes magnesuria, the mechanism is unclear [79]. Serum total Mg levels are inversely correlated with the fasting blood sugar level in diabetics in whom glycosuria, ketoaciduria, and hypophosphatemia contribute to renal Mg wasting [98]. Primary [99] and secondary [100] hyperaldosteronism are associated with renal Mg wasting secondary to volume expansion, causing increased tubular flow rates and decreased NaCl reabsorption [99]. The exact mechanism, however, remains controversial. Other hormonal conditions associated with hypomagnesemia are the syndrome of inappropriate antidiuretic hormone secretion [101] and hyperthyroidism [102].

Redistribution of Mg

“Hungry bone syndrome” after parathyroidectomy [103] or diffuse osteoblastic metastasis [104] can result in hypomagnesemic, hypocalcemic tetany from osseous deposition of Mg and Ca. Epinephrine and other β-agonists (e.g., salbutamol) cause transient hypomagnesemia in healthy subjects [105]. This is thought to occur from uptake of Mg into adipose tissue as fatty acids are released. Release of fatty acids into the blood may also lead to the formation of insoluble fatty acid–Mg2+ and fatty acid–Ca2+ complexes [40]. Massive blood transfusion (>10 U/24 h) may cause hypomagnesemia from the chelating effects of citrate [106]. Hypomagnesemia occurs during and after cardiopulmonary bypass surgery [84, 107]. Potential mechanisms include hemodilution from large-volume infusion of Mg-free fluids, removal of Mg by the bypass pump, and catecholamine-induced intracellular Mg shifts, and binding to free fatty acids [107]. A retrospective study of 30 patients undergoing elective cardiopulmonary bypass surgery demonstrated ionized hypomagnesemia in 73% [108]. Of note, the relationship between Mg2+ and Ca2+ during CPB was variable, and Ca2+ levels did not predict Mg2+ levels [108]. Significant hypomagnesemia (i.e., serum total Mg level <1.40±0.15 mEq/l) occurs in up to 30% of alcoholics. Multiple mechanisms are likely, including decreased Mg intake accompanying poor nutritional status, vomiting, chronic pancreatitis-induced steatorrhea, and Mg malabsorption [109].

Collectively, the above data indicate that hypomagnesemia (serum total Mg level <1.5 mEq/l) may have multiple causes in the ICU patient. Even so, three critical questions remain: (a) to what extent does ionized hypomagnesemia parallel reductions in serum total Mg levels and in total body Mg stores? (b) Does Mg replacement to correct levels of serum total Mg also correct ionized hypomagnesemia? (c) Is correction of serum total or ionized hypomagnesemia associated with definable clinical changes in biochemistry, electrophysiology, inflammatory responses or organ function? Until the answers to these questions are forthcoming, we may be spending considerable effort and expense merely to make serum total Mg levels “look better.”

**Mg, sepsis, and shock**

Novel immunoregulatory effects of Mg deficiency and supplementation are increasingly reported [110, 111,
Ca\textsuperscript{2+} from the sarcoplasmic reticulum of frog myocytes have been found to be correlated with efflux of cellular Ca\textsuperscript{2+} entry during shock. Lower Mg\textsuperscript{2+} concentrations have been found to be correlated with efflux of Ca\textsuperscript{2+} from the sarcoplasmic reticulum of frog myocytes over a 0.3- to 3-mmol concentration range of Mg\textsuperscript{2+} [114]. A direct effect of low [Mg\textsuperscript{2+}], to increase the voltage-gated calcium current (I\textsubscript{Ca}) was implicated. Based on this and other reports [115], Mg\textsuperscript{2+} deficiency may promote abnormal cellular Ca\textsuperscript{2+} entry during sepsis; this may in turn increase free cytosolic and mitochondrial Ca\textsuperscript{2+} to cause cell death. In support of this, intracellular Mg have important, albeit clinically occult protective effects of Mg replacement from endotoxin challenge [118]. Since considerable intracellular Mg\textsuperscript{2+} is complexed to ATP, sepsis, or ischemia/reperfusion-induced ATP hydrolysis or falls in ATP production release intracellular Mg\textsuperscript{2+} ions. Subsequently [Mg\textsuperscript{2+}], concentrations rise, and Mg\textsuperscript{2+} effluxes from cells [115, 117]. Three negative consequences may result: (a) impaired Na\textsuperscript{+}-K\textsuperscript{+} ATPase pump activity, (b) reduced inwardly rectifying K\textsuperscript{+} ion channels, and (c) dysfunctional cell membrane and sarcolemmal Ca\textsuperscript{2+} ion channels [61]. These changes may partly account for the increased lethality of endotoxia seen in rats during hypomagnesemia as well as the protective effects of Mg replacement from endotoxin challenge [118]. Mg\textsuperscript{2+} ions mediate key immunological functions, including macrophage activation, leukocyte adherence, and bactericidal activity [119], granulocyte oxidative burst, lymphocyte proliferation, and endotoxin binding to monocytes [118]. In Mg-deficiency models time-dependent increases are seen in circulating interleukin-1, tumor necrosis factor-\alpha, interferon-\gamma, substance P, and calcitonin gene related peptide [110, 112, 120]. Such effects may result from altered DNA binding of transcription factors notable for their suppression of inflammatory cytokine gene activation, including the cyclic AMP response element binding protein [42]. Likewise, Mak et al. [121] reported overproduction of nitric oxide in an Mg-deficient rat model. In that report increased nitric oxide production was considered secondary to Mg deficiency-related stimulation of inducible nitric oxide synthase and activation of Ca-sensitive nitric oxide synthase from increased intracellular Ca\textsuperscript{2+}. Cytotoxic effects of NO include those resulting from its combination with superoxide to form peroxynitrite [121]. Inhibition of mitochondrial respiration, interference with the O\textsubscript{2} carrying ability of hemoglobin and myoglobin due to interaction with heme proteins, and inhibition of enzymes containing heme and nonheme iron-sulfur centers all contribute to toxicity [122]. Overall, emerging data showing interrelated links among biochemical, physiological, and immunoregulatory effects of Mg deficiency during sepsis and shock suggest the corollary thesis that titrated Mg supplementation can alter outcomes. Further experimental and clinical data are needed to confirm this notion.

**Ionized Mg and intensive care**

Serum total Mg levels are not correlated with serum Mg\textsuperscript{2+} in the critically ill because of accompanying variations in plasma protein concentrations, acid-base balance, metabolic derangements, and drugs that affect Mg balance [58, 123]. Külpmann et al. [123] showed that reduced serum total Mg concentrations may reflect “pseudohypomagnesemia” from hypoalbuminemia when concomitant Mg\textsuperscript{2+} concentrations are normal. Such findings have led to the suggestion that the terms hypo-, normo-, and hypermagnesemia should be restricted to Mg\textsuperscript{2+} levels. Of note, [Mg\textsuperscript{2+}] levels are correlated well with serum Mg\textsuperscript{2+} by \textsuperscript{31}P-nuclear magnetic resonance spectroscopy [124]. In aortic endothelium [Mg\textsuperscript{2+}], levels change within 5 min of increasing extracellular Mg\textsuperscript{2+}, suggesting that extracellular Mg\textsuperscript{2+} dynamically equilibrates with [Mg\textsuperscript{2+}], [125]. Additional studies are needed to confirm whether extracellular Mg\textsuperscript{2+} accurately tracks total body Mg balance. In spite of in vitro studies demonstrating the superiority of ionized Mg measurements over total Mg estimations; few studies have attempted to demonstrate the importance of measuring ionized Mg levels in the critical care setting and to examine the correlation of ionized hypomagnesemia with clinical manifestations and outcomes.

Salem et al. [126] measured Mg\textsuperscript{2+} and serum total Mg concentrations in 180 critically ill patients. Serum total Mg values were sensitive (75%) but not specific (38%) in predicting ionized hypomagnesemia. Increased supraventricular and ventricular dysrhythmias, seizures, hypotension, and death were associated with ionized hypomagnesemia (normal range 0.52–0.60 mmol/l). Recently, Huijgen and colleagues [127] evaluated the relationships between serum Mg\textsuperscript{2+}, total body Mg estimated by Mg content in blood mononuclear cells and erythrocytes, serum albumin, and 30-day mortality in 115 critically ill patients. A normal serum Mg\textsuperscript{2+} was found in 71% of patients with total serum hypomagnesemic values. Moreover, neither total nor ionized Mg measurement was correlated with cellular Mg levels or with outcome. With respect to the cardiovascular effects of hypomagnesemia, Kasaoka et al. [128] found that supraventricular and ventricular extrasystoles decreased by 50% and ventricular...
increased serum Mg²⁺ from 0.35±0.06 mmol/l to 0.54±0.09 mmol/l. MgSO₄ had no effect in patients with a normal serum Mg²⁺. The ratio of Mg²⁺ to Ca²⁺ as a modulator of vascular tone also increased after intravenous MgSO₄ and was thought to contribute to the antiarrhythmic effect. Bertschat et al. [129] determined serum Mg²⁺ levels on days 1, 2, 3, 5, and 7 after myocardial infarction in 42 patients, in addition to concomitant serum total Mg, free fatty acids, Ca²⁺, and total Ca. Compared with serum total Mg concentrations, Mg²⁺ levels fell on the 1st day of myocardial infarction and were inversely correlated with serum free fatty acids. The ionized hypomagnesemia was attributed to β-adrenergic induced lipolysis and binding of Mg²⁺ by fatty acids. Since the benefit of intravenous MgSO₄ during acute myocardial infarction is not established, the authors suggest that serum Mg²⁺ rather than total Mg be measured in coronary care patients, and that those with ionized hypomagnesemia be treated [129].

Frankel et al. [130] noted a poor correlation between serum total and Mg²⁺ values in 113 trauma patients, although injury severity or blood ethanol levels did not predict ionized hypomagnesemia. It has been hypothesized that decreased serum Mg²⁺ levels after trauma result from increases in circulating catecholamines and corticosteroids, and to Mg redistribution within injured tissues [131]. Ionized hypomagnesemia occurs after experimental head trauma [132] and in brain-injured patients [133]. In vivo animal studies have shown that pre- or posttreatment with MgCl₂ 15 min after cerebral injury restores brain Mg²⁺ levels, improves motor function [134], attenuates cognitive deficits [135], and reduces cerebral edema [136]. In a traumatic brain injury rat model Bareyre et al. [137] studied serum Mg²⁺ levels 24 h postinjury and neuromotor outcome after 1 and 2 weeks. Supplemental Mg treatment given to rats with ionized hypomagnesemia reduced posttraumatic impairments. No such correlation was found using blood total Mg levels, which did not change postinjury. In other in vivo animal studies Mg treatment has been shown to reduce posttraumatic edema and cortical damage, in association with concomitant changes in gene expression for c-fos, heat shock protein-70, neurotrophins, and cyclooxygenase-2 [136, 138]. In addition to Mg's multiple effects on intermediary metabolism, oxidative phosphorylation, protein synthesis, regulation of membrane permeability to Ca²⁺ and K⁺ ions, and potential anti-inflammatory effects, it has also been recently shown in murine cortical cell cultures to be a potent antioxidant to iron-dependent oxidative injury [139]. By increasing the physiologically active ionized Mg fraction, MgCl₂ possibly restores the ability of cells to maintain homeostasis [137]. Available data therefore suggest that early measurement of blood ionized Mg levels and supplementa-
Gram-negative bacteremic sepsis when Mg sulfate (MgSO₄) was given using a rapid regimen (8 mmol intravenously over 5 min). The authors did not mention the degree of hypotension that occurred, nor the baseline blood pressure and the use of vasopressors (if any) prior to Mg administration. No hypotension occurred when 48 mmol MgSO₄ was infused over 24 h. Such hypotensive responses may reflect the combined effects of sepsis-induced myocardial dysfunction together with Mg infusion-induced reductions in systemic vascular resistance. In the critical care setting treatment recommendations must therefore be tempered with the urgency of replacing Mg deficits. Slower infusions (mentioned below) are appropriate unless cardiac arrhythmias or seizures are present. Slow replacement can be achieved by giving 8–12 g MgSO₄ intravenously over 24 h, followed by 4–6 g daily for another 3–4 days [40]. Since up to 50% of administered Mg may be lost in the urine, continuous infusions of Mg or repeated doses may be preferable. However, there are no controlled data with regard to the efficacy of this approach in critically ill patients. Oral Mg salts can be used as maintenance therapy in conditions associated with chronic Mg loss, for example, short or long-term use of diuretics. An initial daily dose of 300–600 mg elemental Mg may be used. The Mg is given in divided doses to decrease its cathartic effect. Significant hypermagnesemia can complicate Mg replacement when the glomerular filtration rate is less than 30 ml/min [13]. Elevation in serum total Mg to levels higher than 2 mmol/l are usually accompanied by symptoms. The effects of increasing rise in serum total Mg levels include hypotension (1.5–2.5 mmol/l), electrocardiographic changes (2.5–5 mmol/l), areflexia (5 mmol/l), respiratory paralysis (7.5 mmol/l), and cardiac arrest (>12.5 mmol/l) [38]. Physiological antagonism of hypermagnesemia with intravenous calcium gluconate can be used until dialysis can be initiated.

With respect to cardiac arrhythmias and ventricular arrhythmias in particular, recommended protocols for Mg treatment are unclear as no large-scale controlled studies comparing replacement regimens, their effects on total vs. ionized Mg levels, and clearcut physiological endpoints have been performed. In general, 2 g MgSO₄ constituting 8 mmol intravenously over 1–2 min, followed by an additional 40 mmol over the next 5 h is considered safe and probably effective [141]. As discussed above, an antiarrhythmic dose of 0.15 mmol/kg MgSO₄ given as an intravenous bolus over 10 min was used by Kasaoka et al. [128] to correct ionized hypomagnesemia (<0.40 mmol/l). Simultaneous administration of K⁺ and Ca may be necessary because concomitant losses of these cations are common in Mg deficiency. Emerging data underscore the lack of a predictable relationship between serum total and ionized Mg levels, either before or after intravenous Mg supplementation. Barrera et al. [144] were unable to predict serum Mg²⁺ levels from serum total Mg values in 33 ICU patients, in whom intravenous treatment with 4.1 mmol (1 g) had no effect on ionized Ca²⁺ or K⁺ concentrations, although both serum ionized and total Mg levels were increased.

**Summary**

Mg metabolism and the important physiological roles of Mg as they relate to the critically ill have been reviewed. However, fundamental aspects of Mg metabolism, assessment of Mg deficiency, and efficacy of treatment of hypomagnesemia, whether total or ionized, remain poorly understood. Although serum total Mg continues to be the most frequently used tool for diagnosing and treating hypomagnesemia, randomized clinical studies are needed to determine whether newer methods of Mg assessment, including the measurement of Mg²⁺, are superior. Newer insights into the immunomodulatory roles of Mg in vivo, improvements in estimating whole-body and compartmental Mg concentrations, and clearer documentation of the biochemical and physiological effects of correcting hypomagnesemia will undoubtedly assist the intensivist in determining the rationale and the mode for correcting a low Mg value.

**References**
