Hypomagnesaemia in Adults - Full Clinical Guideline

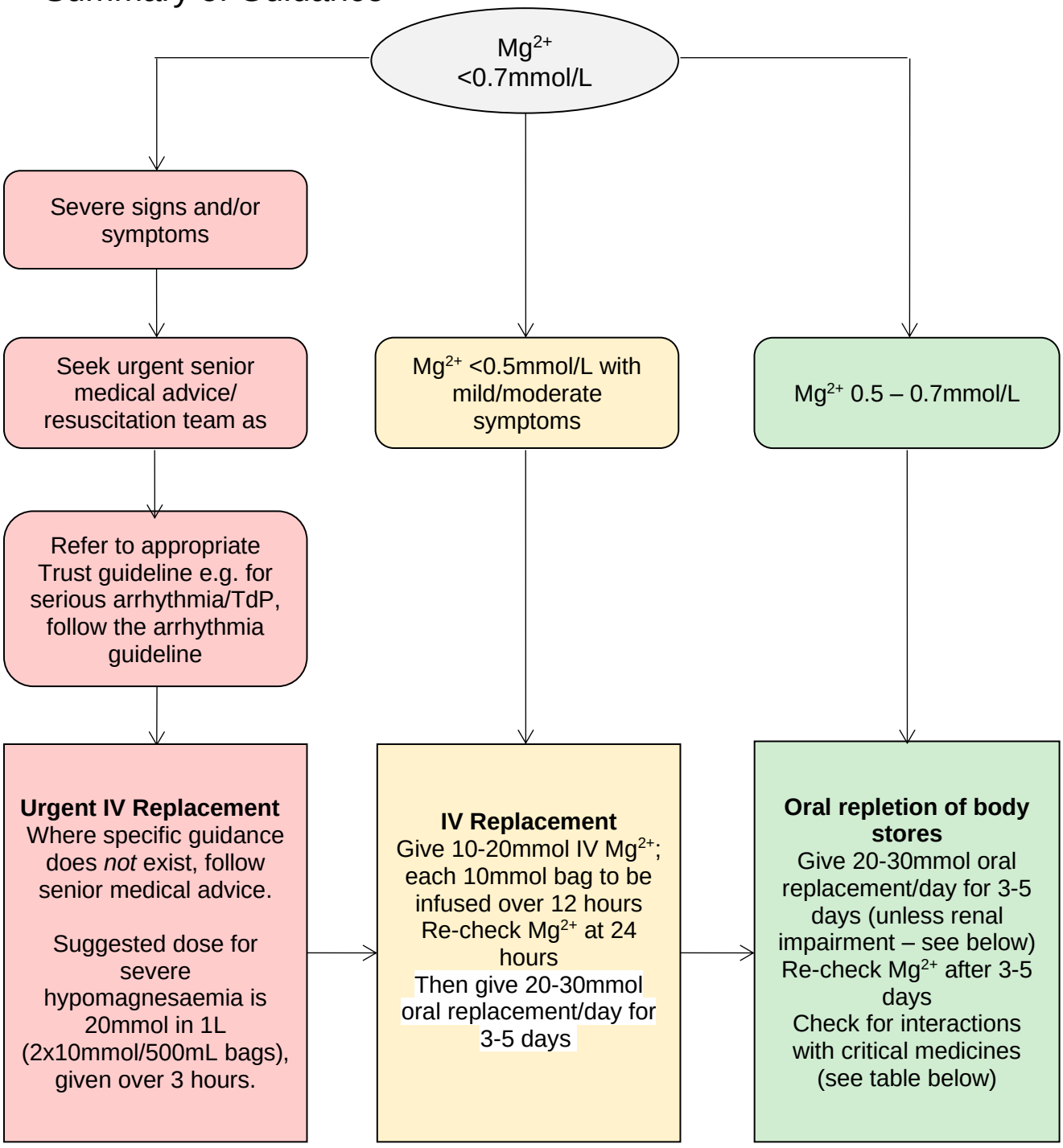
Reference no: CG-T/2023/161

Contents

Note: this guideline does **not** apply to the following**: -**

- **Critical care areas** – see unit specific guidance on Koha or locally.
- **Severe ventricular arrhythmias** secondary to hypomagnesaemia – see the 'Arrhythmias' guidance on Koha**.**
- **Refractory VF/VT arrest with suspected hypomagnesaemia** – follow resuscitation monographs
- **Pre-eclampsia/eclampsia** – see separate guidance on Koha**.**
- **Acute exacerbations of asthma** – see separate guidance on Koha**.**
- **High Stoma Output** patients- see separate guidance on Koha

Summary of Guidance



Magnesium sulfate is available in the following forms at RDH:

- $MgSO_4$ 10mmol in 500mL NaCl 0.9%
- $MgSO_4$ 10mmol in 100mL NaCl 0.9% (restrict use to fluid restricted patients)

At QHB infusions should be prepared in accordance with MediTech instructions.

$MgSO_4$ is compatible in glucose 5% - consider use in hypernatraemic patients – contact pharmacy if required.

NB: Each 1g of magnesium sulfate (as heptahydrate) is equivalent to approximately 4 mmol magnesium (Mg^{2+})

Definition

Serum magnesium <0.7mmol/L (clinically apparent signs and symptoms generally not seen until <0.5mmol/L)

Incidence

Common disorder; seen in up to 12% of hospitalised inpatients, rising to 60-65% of critically unwell patients in intensive care.

Clinical Presentation

Most patients are asymptomatic until Mg^{2+} levels are <0.5mmol/L – some will remain asymptomatic even with severe hypomagnesaemia. Signs and symptoms are non-specific, and generally reflect the physiological roles of Mg^{2+}:

- Biochemical abnormalities:
    - **Hypokalaemia** (concurrent in 40-60% of cases) – shared underlying causes, but also evidence that low Mg^{2+} leads to increased renal K^{+} wasting.
    - **Hypocalcaemia** – low Mg^{2+} leads to PTH resistance and a decrease in PTH secretion, resulting in hypocalcaemia.
    - **Note**: the above abnormalities are often difficult to correct until magnesium levels have been normalised. Therefore the hypomagnesaemia should be treated first, or concurrently.
- **Neuromuscular irritability** similar to that seen in hypocalcaemia. As above, hypocalcaemia is often present with hypomagnesaemia, and may contribute.
    - Tetany – patients may develop positive Trousseau and Chvostek signs, muscle spasms and muscle cramps.
    - Seizures – can be generalised tonic-clonic in nature, or multifocal motor.
    - Dyskinesias – such as athetosis, or choreiform movements.
    - Vertical nystagmus – rare, but diagnostically useful, as in the absence of structural cerebellar/vestibular pathology the only other causes are severe hypomagnesaemia and Wernicke's encephalopathy.
- Cardiovascular effects such as **tachycardia, hypertension,** or **ventricular arrhythmias** (partly related to associated hypokalaemia)

- **ECG changes**: Symptomatic patients should have an ECG to search for characteristic changes associated with hypomagnesaemia. Mild to moderate hypomagnesaemia causes widening of the QRS complex, prolongation of the QT interval, and peaking of T waves. More severe depletion leads to further widening of the QRS complex, prolongation of the PR interval, and diminishing of T waves.

Patients with a history of ischaemic heart disease are at particular risk of ventricular arrhythmias, which include extrasystolic beats, ventricular fibrillation, and ventricular tachycardias (including torsades de pointes). Extra caution is required in patients taking anti-arrhythmics, due to the risk of concurrent hypokalaemia and associated QT-prolongation.

Assessment of magnesium status

Low serum magnesium *generally* indicates total body depletion, however, serum magnesium levels correlate poorly with tissue levels and do not reflect total body magnesium levels (similar to calcium). Therefore patients with depleted intracellular stores may have normal serum levels. Additionally, only free-ionised Mg^{2+} is biologically active, but tests reflect total serum magnesium levels; hypoalbuminaemic states may therefore result in spurious hypomagnesaemia due to the increased free-fraction of Mg^{2+}. Despite these limitations, serum magnesium is the method of choice in assessing acute magnesium status, owing to its ease and low relative cost.

Causes of hypomagnesaemia

Drugs

- Proton-pump inhibitors – likely reduce intestinal Mg^{2+} absorption. Exact incidence is unknown, but prospective studies are lacking. Most cases occur with longer term use (>1 year), though cases have also occurred ≥3 months after starting treatment. Risk appears to be greatest in those receiving concomitant diuretics.

- Systemic anti-cancer therapies (SACT), particularly those targeting the epidermal growth factor receptor (EGFR):
    - Cetuximab
    - Eribulin
    - Cisplatin
- Antimicrobials
    - Foscarnet (15% incidence – causes renal wasting)
    - Aminoglycosides (gentamicin/amikacin)
- Diuretics (the degree of hypomagnesaemia induced by loop and thiazide diuretics is generally mild)
    - Loop diuretics (e.g. furosemide, bumetanide)
    - Thiazides (e.g. bendroflumethiazide, indapamide)

- NB: Potassium sparing diuretics (e.g. amiloride) lower Mg^{2+} excretion, and are not associated with hypomagnesaemia
  - In patients with hypomagnesaemia 2° to loop/thiazide diuretics, where these diuretics cannot be stopped – addition of a potassium sparing diuretic should be considered to minimize renal Mg^{2+} losses.

Nutritional

- Severe dietary deficiency (the amount of Mg^{2+} in the Western diet has decreased by 30-40% over the previous 30 years, likely due to increased processing).
  - Patients with a history of diabetes or ethanol excess are especially susceptible to low dietary intake.

Gastro-intestinal

- Secretory diarrhoea: upper GI secretions contain 0.5mmol/L Mg^{2+}, lower GI secretions contain 7.5mmol/L Mg^{2+}.
  - Any condition that increases GI losses will increase magnesium loss, e.g. gastroenteritis, IBD, prolonged NG suction)
- Malabsorption e.g. short bowel syndrome, severe coeliac disease.
- Pancreatitis (due to saponification in necrotic tissue)

Endocrine

- Metabolic acidosis (diabetic, alcoholism, starvation)
- Osmotic diuresis – common in diabetic patients (excess glucose, DKA)
- Hypoparathyroidism/hyperthyroidism
- Hungry bone syndrome (post-parathyroidectomy/thyroidectomy)

Renal

- A range of genetic conditions such as Gitelman's syndrome or Bartter's syndrome can lead to primary magnesium wasting.
- Post-obstruction/acute tubular necrosis (diuresis following recovery can lead to Mg^{2+} wasting)

Treatment

Principles

1. IV replacement should be reserved for patients who are symptomatic, have serious clinical signs of hypomagnesaemia, or are unable to tolerate oral replacement. **Pre-diluted, ready-made infusions should be used wherever possible.**

2. Mg^{2+} is *slowly* equilibrated into body stores - high serum levels lead to rapid increases in renal excretion (patients with normal renal function can readily

excrete >200mmol Mg^{2+} per day in the urine). Thus, ***rapid IV replacement will lead to up to 50% of the magnesium load being rapidly excreted into the urine***.

3. Rapid infusion can cause respiratory depression, hypotension, and bradycardia. In emergencies, where rapid rates are being used, patients should be monitored closely for signs of hypermagnesaemia and undergo ECG monitoring. The rate should be reduced if bradycardia occurs.
4. Doses should be reduced by 25-50% in patients with renal impairment, and Mg^{2+} levels monitored more frequently. In patients with severe impairment, seek advice from the renal team.
5. Co-magaldrox is the oral formulation of choice in the majority of patients, due to the following:
    a. As oral Mg^{2+} is incompletely absorbed, high doses can commonly cause osmotic diarrhoea. Co-magaldrox also contains Al^{3+} which is constipating, and therefore using the two together theoretically reduces diarrhoea associated with Mg^{2+} alone.
    b. No clinically relevant differences in oral Mg^{2+} absorption are expected for different salts of magnesium (e.g. hydroxide/citrate/aspartate).
6. Oral magnesium supplementation can reduce absorption of other oral medication to a clinically relevant extent – see table below.

Dosing

Indication	Treatment
Mg^{2+} <0.5mmol/L with severe signs or symptoms	1. Treatment as per the relevant guidelines (e.g. arrhythmias) 2. Where specific guidance does not exist, follow senior medical advice – consider giving 20mmol over three hours. 3. Give further replacement to replenish body stores, as for mild/moderate symptoms below. (At RDH a pharmacist is available on the resus team 24/7. Crash bleep via 2222, asking for pharmacist, if IV $MgSO_4$ is needed in an emergency)
Mg^{2+} <0.5mmol/L with mild/moderate symptoms	1. Give 10-20mmol magnesium sulfate IV over 12-24h (each 10mmol bag over 12h, where possible) 2. Then give 20-30mmol oral replacement/day for 3-5 days

Mg^{2+} <0.7mmol/L and asymptomatic	1. Give 20-30mmol oral replacement/day for 3-5 days

Oral Formulations

Formulation	Co-magaldrox (Maalox® or Mucogel®)	Magnesium-L-Aspartate (Magnaspartate®)
Licensing	Licensed product – use for hypomagnesaemia is off-label	Licensed for hypomagnesaemia
Place in Therapy	1st Line for acute replacement of hypomagnesaemia. Do not use in severe renal impairment.	2nd line if co-magaldrox not appropriate: i.e. severe renal impairment/need for long term supplementation
Mg^{2+} Content	5mL of suspension: ≈3.4mmol	One 6.5g sachet: 10mmol
Recommended Dosing (normal renal function)	10mL TDS/QDS	1 sachet BD/TDS
Oral Administration	Shake well before use.	Disperse one sachet in 50-200mL of water, tea or orange juice.
Enteral feeding tube administration	**Not** recommended. Al^{3+} likely to form protein complexes with enteral feed and block tube/ form oesophageal plug.	Suitable. Disperse one sachet in 200mL of water and administer through the enteral tube. Flush well post-dose. Prolonged break in feeding not required pre/post-dose. Increased risk of osmotic diarrhoea if given via tubes terminating in the jejunum.
Cautions	Product contains Al^{3+}: • PO_4^{2-} binder – may cause hypophosphataemia if given long term • Risk of Al^{3+} accumulation in renal impairment (especially if given with citrates/ascorbic acid containing products – dispersible tabs/citric fruit juice)	
Side effects	Uncommon: Diarrhoea/constipation	Uncommon: Diarrhoea

Drug interactions with oral magnesium

- Co-magaldrox may interact to a greater extent than magnesium aspartate for certain medication – speak to a pharmacist for advice.
- Data doesn't exist for all medication: a general rule should be to try to separate administration of co-magaldrox/magnesium as much as possible from other orally administered drugs.
- The table below is *not* exhaustive – seek pharmacist advice before prescribing oral magnesium for a patient on enterally administered critical medication (e.g. anti-retrovirals, immunosuppressants etc.)

Drug	Interaction	Action
Quinolones	Ciprofloxacin: 85% reduction Levofloxacin: 45% reduction	Give the quinolone 2h before, or 4-6h after the Mg^{2+}
Tetracyclines	Doxycycline: 100% reduction IV doxycycline: 36% reduction Tetracycline: 90% reduction Oxytetracycline: 50% reduction	Seek pharmacist advice, consider alternatives. If concurrent use necessary, separate administration by >2-3h or use IV Mg^{2+}
Nitrofurantoin	Variable, uncertain clinical importance	Separate administration by >2h if possible. Monitor for effect
Rifampicin	Uncertain, 20-35% reductions reported	Give rifampicin 1h before co-magaldrox
HIV Medication	Variable, but of obvious clinical importance	Seek pharmacist advice
Bisphosphonates	Marked reduction (likely 90-100%)	Give PO bisphosphonates at least 60 minutes before
Tyrosine Kinase Inhibitors	Variable	Seek pharmacist advice
Levodopa	Appears to affect MR preparations only: 32% reduction in absorption reported	Separate dosing by 1-2h and monitor for worsened PD symptoms
Ascorbic acid (Vitamin C)	Increased Al^{3+} absorption from co-magaldrox – potential for aluminium toxicity in patients with poor renal function	Avoid concurrent use. Co-magaldrox should be avoided in severe renal impairment. Use Magnaspartate® sachets instead.

Citrates (e.g. orange juice, simple linctus, oral rehydration solutions, **effervescent drugs**)	Increased (5-50 fold) Al^{3+} absorption from co-magaldrox – potential for aluminium toxicity. Fatalities reported in advanced renal impairment.	Avoid concurrent use. Co-magaldrox should be avoided in severe renal impairment. Use Magnaspartate® sachets instead.
Oral phosphate (Phosphate Sandoz®)	Reduced phosphate absorption with co-magaldrox	Separate administration by ≥2h where possible

Intravenous Administration

Available pre-diluted formulations:	• Magnesium sulfate 10mmol in 500mL NaCl 0.9% • Magnesium sulfate 10mmol in 100mL NaCl 0.9% Note that magnesium sulfate is also compatible in glucose 5%. Consider using glucose 5% as a diluent in patients who are hypernatraemic (Na^+ content of those made in 0.9% saline: 500mL ≈ 77mmol, 100mL ≈ 15mmol).
Dose equivalence:	**Each 1g of magnesium sulfate (as heptahydrate) is equivalent to approximately 4 mmol magnesium (Mg^{2+})** **Magnesium sulfate 50% w/v ≡ 2mmol/mL ≡ 500mg/mL ≡ 1g/2mL**
Concentration:	**For peripheral administration**, concentrations should generally not exceed 0.2mmol/mL. In severely fluid restricted patients, where central access is not possible, concentrations up to a *maximum* of 0.8mmol/mL can be considered.
Rate:	Generally, a maximum rate of 0.6mmol/min (36mmol/h) is recommended. As above, rapid administration leads to increased urinary excretion, and increases the risk of hypermagnesaemia.

Alternative Routes of Administration

Intramuscular Administration

Magnesium sulfate can be given intramuscularly, and is licensed via this route. However, it is *painful*, requires multiple sites of injection, and has no therapeutic advantage over the IV route. Thus, use of intramuscular magnesium should be reserved for patients with no IV access, where the oral route is unavailable. The 50% w/v ampoules can be used for this indication, without further dilution. The licensed dose is to give 4-8mmol (2-4mL) IM, every six hours for four doses. In more severe

hypomagnesaemia, a regimen of 1mmol/Kg, given over 24h, in divided doses, has been suggested.

IM doses should not be given into muscles that are emaciated or atrophied. Volumes >5mL will need to be given over multiple injection sites - cachexic, or elderly patients may tolerate smaller volumes (≤2mL).

Subcutaneous Administration

Limited evidence suggests that magnesium sulfate may, with caution, be given by subcutaneous infusion, in individual cases where other routes are impractical or impossible. Published evidence is limited to individual case reports and small trials. Seek pharmacist advice if considering the use of this route.

Further Information

Physiology

99% of total body magnesium resides in bone, muscle, and non-muscular soft tissue. Extracellular magnesium accounts for only ≈1% of total body levels, and similarly to calcium exists in three forms: 1) free-ionised (55-70%), 2) protein-bound (20-30%), 3) anion-magnesium complexes such as $MgSO_4$, $Mg_3(PO_4)_2$ (5-15%).

Intestinal absorption of Mg^{2+} is variable (24-76%) and poorly regulated; the majority of homeostatic regulation of serum Mg^{2+} is performed by the kidneys. Absorption occurs mostly in the small intestine via the paracellular route, though an important fraction is absorbed in the colon via active transport. Intestinal absorption is proportional to body magnesium status, rather than dietary intake.

Serum Mg^{2+} levels are closely related to bone metabolism. 50-60% of total body magnesium resides as a key surface component of the hydroxyapatite mineral structure of bone. Around one-third of this magnesium is readily available for exchange with that in the plasma and bone thus provides a crucial buffer to acute changes in plasma concentration.

The kidneys are the primary homeostatic regulators of serum magnesium levels. Approximately 2.4g/day of magnesium is filtered at the glomerulus. Typically ≈95% of this is reabsorbed, though the kidney is capable of controlling the degree of re-absorption within a sizable range (30-99.5%). Magnesium is handled throughout the nephron as follows:

- 70-80% of plasma magnesium is ultra-filterable at the glomerulus (free-ionised & complexed)
- 15-25% is immediately reabsorbed in the proximal tubule along with Na^+ & H_2O via a passive, paracellular process.

- Unlike most other electrolytes, the majority of Mg^{2+} (65-75%) is reabsorbed in the thick ascending limb (TAL) of the loop of Henle via the paracellular route (mediated by claudin-16 & 19)
- 5-10% (70-80% of that remaining) of Mg^{2+} is reabsorbed in the distal convoluted tubule via transient receptor potential melastatin-six (TRPM-6). Although the amount absorbed is lower than more proximal segments, *homeostatic regulation at this stage is essential, as it determines final urinary Mg^{2+} losses.*

Mg^{2+} status is the major regulator of TRPM6 expression and therefore urinary excretion. Hormonal control (e.g. angiotensin-II, aldosterone, insulin) appears to play only a minor role, with the exception of oestrogen, which increases TRPM-6 expression, and thereby, reabsorption.

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