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## MANAGEMENT OF HYPERCALCAEMIA

Hypercalcaemia is a serum, albumin-corrected, Calcium Concentration (s[Ca]) of  $\geq 2.6$  mmol/L on two occasions, at least one week apart<sup>[1,2]</sup>. It is the commonest metabolic disorder associated with malignancy; occurs in 10–15% of patients. Early recognition of hypercalcaemia is crucial – it has high morbidity and is potentially life threatening<sup>[1,2,4]</sup>. Prompt treatment results in excellent outcomes<sup>[3]</sup>. Management depends on a careful history and physical examination and a purposeful selective approach to investigations<sup>[1,4]</sup>.

**Causes: (Commonly caused by PHPT and Malignancy in >90% cases<sup>[1,2,4,5]</sup>)**

<p><b>PTH:</b> inappropriately normal or high &gt;1.5 pmol/L</p>	<p>a. <b>PHPT: the commonest cause, &gt;50% of all cases<sup>[1,4,6,7]</sup></b>                      b. Familial Hypocalcaemic Hypercalcaemia (FHH)<sup>[1,4,6,7]</sup>                      (Consider endocrine opinion for further evaluation)                      c. THPT in CKD<sup>[6]</sup>.</p>
<p><b>PTH:</b> suppressed &lt;1.5 pmol/L (i.e. non-PTH mediated)</p>	<p>1. <b>Malignancy-Associated Hypercalcaemia (MAH):</b> the second commonest cause<sup>[1,2,5-7]</sup>. Usually severe. Commonest causes are lung, breast and haematological cancers<sup>[2,5]</sup>. A late, poor prognostic sign.                      2. Drugs: excess VD/Ca<sup>2+</sup> intake; lithium, oestrogens, progestogens, tamoxifen, <b>thiazides</b>, vitamin A excess (OC-mediated bone resorption)<sup>[1-7]</sup>.</p>

	<ol style="list-style-type: none"> <li>3. Granulomatous disease (activation of extra-renal <math>1\alpha</math>-hydroxylase <math>\rightarrow</math> increased calcitriol): e.g. sarcoidosis, Tuberculosis, IBD<sup>[1,2,4,6]</sup>.</li> <li>4. Others: CKD (calcium-based Pi binders +/- VD, +/- adynamic bone disease), adrenal insufficiency, thyrotoxicosis (stimulate osteoclastic bone resorption), immobilisation<sup>[1-7]</sup>.</li> </ol>
<b>Symptoms and Signs (S/S)</b> <sup>[1-10]</sup>	
<p>The extent of hypercalcaemia-associated S/S relates to the severity and rate of onset of hypercalcaemia. Asymptomatic or non-specific S/S if mild and/or chronic. Symptoms include the mnemonic 'Stones, Bones, Abdominal moans and Psychic groans':</p> <ul style="list-style-type: none"> <li>● <b>Skeletal:</b> bone pain, fractures (osteoporotic in HPT or pathological in malignancy).</li> <li>● <b>Neuropsychiatric an Neuromuscular:</b> anxiety, depression, muscle weakness (lethargy, confusion and coma – in patients with severe rapidly increasing s[Ca]).</li> <li>● <b>Gastrointestinal:</b> constipation, nausea, vomiting (dehydration), abdominal pain, pepticulcer and pancreatitis.</li> <li>● <b>Renal:</b> polyuria, polydipsia, and dehydration (<b>N DI</b>), renal colic (nephrolithiasis) and renal impairment (nephrocalcinosis) and dRTA</li> <li>● <b>CVS:</b> acute – shortened QT interval, arrhythmias are rare. Chronic – hypertension, deposition of calcium in heart valves, coronary arteries and myocardial fibres.</li> <li>● <b>Other:</b> itching, keratitis, conjunctivitis and corneal calcification.</li> </ul>	
<b>Investigations</b> <sup>[1,2,4,5]</sup>	
<ul style="list-style-type: none"> <li>● s[Ca], Albumin, UEs. Repeat after one week to confirm the result.</li> <li>● <b>Intact PTH (iPTH): the single most important diagnostic test</b></li> <li>● Clinically-guided tests to identify the underlying cause <b>if iPTH suppressed:</b> <math>\uparrow</math>PTHrP (possibly carcinoma lung), <math>\uparrow</math>ALP (osteolytic HrC – possibly carcinoma breast), VD metabolites, Igs/SEP, TSH.</li> </ul>	
<p><b>Abbreviations:</b> PHPT=Primary Hyperparathyroidism; N DI=Nephrogenic Diabetes Insipidus; dRTA=Distal Renal Tubular Acidosis; VD=Vitamin D; IBD=Inflammatory Bowel Disease;</p>	

**Treatment** choice depends on the severity and rate of onset of hypercalcaemia, in addition to the symptoms and the underlying cause. Managing hypercalcaemia is based mainly on clinical experience and accepted practice rather than controlled trials<sup>[3]</sup>.

Calcium level	Treatment <sup>[1-12]</sup>
<p><b>Mild</b> 2.65–2.9 (Asymptomatic)</p> <div style="border: 1px solid black; padding: 2px; width: fit-content;">                     Almost All patients                 </div>	<ol style="list-style-type: none"> <li>1. Prompt identification and treatment of the underlying cause – stop thiazides and any vitamin A, D or Ca supplements.</li> <li>2. Immediate treatment not usually necessary<sup>[5]</sup>. Refer to endocrine or other teams as appropriate<sup>[1,4]</sup>.</li> <li>3. Monitor: repeat s[Ca] after one week <b>if the cause is unconfirmed</b>. (Fast increasing s[Ca] suggest malignancy; refer urgently<sup>[2]</sup>).</li> <li>4. Ensure adequate <b>oral fluid</b> intake<sup>[2]</sup>; will also promote renal Ca excretion– avoid excessive fluid loading<sup>[1,2,7]</sup>. Caution in cardiac, renal disease and old age<sup>[2]</sup>.</li> </ol> <p style="background-color: #e0f0ff; padding: 5px;">Asymptomatic, mild hypercalcemia is often discovered on routine screening: patients generally do not benefit from normalisation of s[Ca]<sup>[4,6]</sup>.</p>

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<b>Moderate</b> <b>3.0–3.4</b>	<b>Asymptomatic</b> – Apply all treatment measures listed above
	<b>Symptomatic</b> – treat as severe hypercalcaemia, box below
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<b>Severe</b> <b>≥3.5</b> All patients	<ul style="list-style-type: none"> <li>• Apply all treatment measures listed above +</li> <li>• Immediate admission to hospital<sup>[1–3,6,7]</sup>.</li> <li>• Rehydration to achieve euvolaemia: IV 0.9% normal saline (NS) ~ 3–4L/24hrs<sup>[1,3,5–7,12]</sup>. Continue with IV NS as necessary. Caution – avoid excessive fluid loading as above<sup>[1,2,7]</sup>.</li> <li>• <b>Zoledronic Acid*</b> (ZA) 4mg in 100ml 0.9% NS infusion over 15 minutes – superior (more efficacious + longer duration of action) to pamidronate for MAH<sup>[1,3,5,6,11,12]</sup>; complete normalisation of s[Ca] levels in &lt; three days in 80–100% of patients<sup>[1]</sup>.</li> <li>• Monitoring: daily s[Ca], [Mg], [Pi] and UEs</li> <li>• Give <b>Calcitonin</b> if symptoms are severe (see further treatments)</li> </ul> <p>Loop Diuretics (LD): their routine use is not indicated<sup>[1,3,5,12]</sup>. Judicious use of loop diuretics if volume overload develops inadvertently<sup>[1,3,5,12]</sup>.</p>
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<b>Further treatments</b> <b>All patients</b>	
<ul style="list-style-type: none"> <li>• <b>Calcitonin</b>: has the most rapid onset of action, within 4–6hrs. Give alongside ZA, dose 4µg/kg, im or sc, 6–12 hourly. It lowers s[Ca] by ~ 0.5mmol/l. The effect is short, lasts for few hours. Use for a maximum of 48hrs, limited efficacy thereafter because of tolerance<sup>[1–6,12]</sup>.</li> <li>• <b>Dialysis (HD/PD)</b>: consider for severe (s[Ca] 4.5 to 5mmol/L), refractory hypercalcaemia with neurologic symptoms and stable circulation or in those with severe hypercalcaemia complicated by renal failure<sup>[1,3–7]</sup>.</li> </ul>	
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<b>Further: Cause-specific treatment</b>	
<ul style="list-style-type: none"> <li>• <b>PHPT</b>: surgical treatment is indicated for all patients with specific PHPT-related symptoms<sup>[9]</sup>. Cinacalcet is accepted in PHPT where surgery is indicated but clinically inappropriate<sup>[1,2]</sup>. Cautious correction of vitamin D deficiency, to levels of 50–75nmol/l<sup>[1,2,9]</sup>; and bisphosphonates for osteoporosis<sup>[2]</sup>.</li> <li>• <b>MAHs</b>: admit if moderate, severe or symptomatic hypercalcaemia and treat as above<sup>[1,2,5]</sup>. If severe, symptomatic MAH refractory to ZA, consider <b>denosumab</b><sup>†</sup> - initial dose 60mg subcutaneously, with repeat dosing based upon response<sup>[1,5]</sup>. Further, see notes below.</li> <li>• <b>Granulomatous disease</b> (secondary to calcitriol excess); <b>haematological malignancy: glucocorticoides</b> (Prednisolone 20–40mg orally daily), effective within 2–5 days<sup>[1,3,5–7]</sup>. Calcitriol excess responds poorly to bisphosphonates.</li> </ul>	
<p><b>Abbreviations:</b> UOP=Urine Output; HD=Haemodialysis; PD=Peritoneal Dialysis</p> <p><b>*Bisphosphonate: Disodium Pamidronate (DSP):</b> an alternative to ZA, 60-90mg in 250ml-1L NS 0.9% IV over 4hrs. Bisphosphonates are effective by the 2nd to 4th day<sup>[5]</sup>. s[Ca] usually returns to normal within seven days.</p>	



## ABC of Intravenous Fluids

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**Renal impairment:** caution, bisphosphonates are excreted by the kidneys<sup>[5]</sup>. No dose adjustment if serum creatinine (sCr)  $\leq 300$ . If sCr  $> 300$  – ensure adequate hydration; give **pamidronate**,  $\frac{1}{2}$  the normal dose at slower rate; repeat in few days if ineffective<sup>[3,5]</sup>. **Side effects of IV bisphosphonates:** include fever, arthralgia, myalgia, fatigue, bone pain, impaired renal function and osteonecrosis of the jaw in association with long term use<sup>[5]</sup>.

### <sup>§</sup>Malignancy-Associated Hypercalcaemia (MAH):

Treat as above. Duration of response to bisphosphonates is 3–4 weeks<sup>[1,2]</sup>. Hence, re-check s[Ca] after two weeks – without treatment of the underlying cancer, hypercalcaemia usually returns 2–4 weeks. ZA can be re-administered as necessary to control hypercalcaemia<sup>[1,2]</sup>. Consider oral Bisphosphonate for recurrent, >three episodes, hypercalcaemia. However, patients with metastatic bone disease usually receive IV ZA or pamidronate every 3–4 weeks as part of their treatment to prevent skeletal complications<sup>[5]</sup>. This measure will also prevent recurrent hypercalcaemia<sup>[1,2,5]</sup>.

**<sup>†</sup>Denosumab:** It is a human monoclonal antibody to the Receptor Activator of Nuclear factor Kappa B Ligand (RANKL), an OC differentiating factor. It inhibits OC formation, decreases bone resorption, increases Bone Mineral Density (BMD), and reduces the risk of fracture. Denosumab is not excreted through the kidneys, hence no restrictions in CKD patients. Beware of the risk of hypocalcaemia<sup>[1,5]</sup>.

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