An elderly woman with muscle cramps and paraesthesia after osteoporosis treatment

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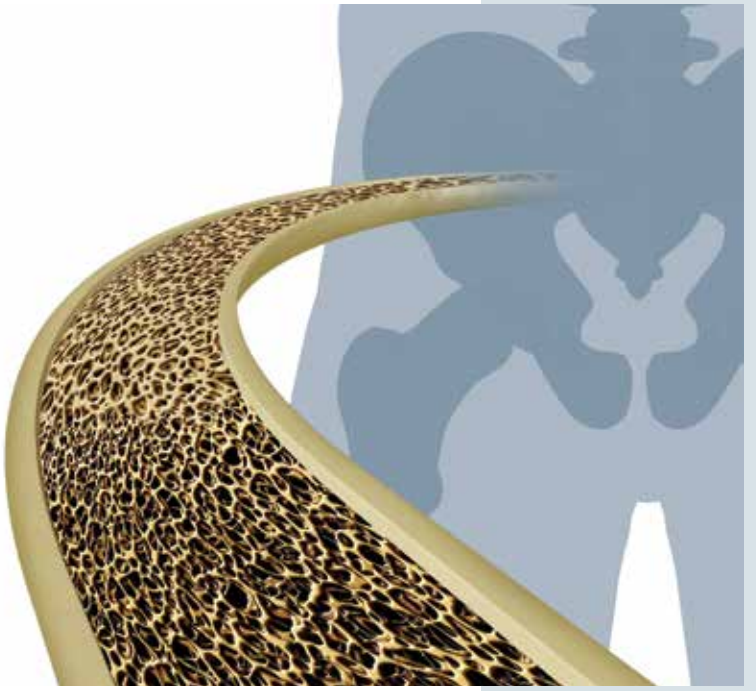
The immediate management and investigation of an acute endocrine presentation in general practice is discussed in this section. It is inspired by, but not based on, a real patient situation.



Nalini is a frail 82-year-old Indian woman who sees you regularly for several medical conditions. She presents to your clinic in early spring complaining of muscle cramps for the past few days and 'tingling' in her fingers and around her mouth. When the practice nurse measures her blood pressure, she develops a spasm in her hand and wrist and the test is aborted.

Nalini has had type 2 diabetes for 30 years, complicated by proliferative retinopathy and nephropathy. She is currently awaiting cataract surgery. She has a history of hypertension (treated with an ACE inhibitor and calcium channel blocker), dyslipidaemia (currently controlled on a statin) and gastro-oesophageal reflux (treated with a proton pump inhibitor). She has memory impairment but still functions independently at home with family support.

Nalini has had several falls, probably related to her frailty, visual impairment and peripheral neuropathy. Nine months ago, she sustained a left femoral neck fracture after tripping over a floor mat. The discharge summary from that admission mentions that the orthogeriatrics team recommended treatment with an antiresorptive agent. Denosumab injection once every six months was suggested, to minimise Nalini's pill burden and because of concerns about compliance and the side effects of oral bisphosphonates, given her history of oesophageal reflux.

It has taken Nalini some time to get back on her feet after being discharged from rehabilitation. A week ago, she received her first injection of denosumab 60 mg.

On examination, she is alert, orientated and in no obvious distress. Her respiratory rate is not elevated. She has intact power, co-ordination and reflexes. Sensation is mildly reduced in her toes. Tapping over the facial nerve elicits twitching around the mouth on the same side (Chvostek's sign).

What is the likely cause of Nalini's symptoms and how will you confirm this?

Answer: Typical symptoms of acute hypocalcaemia are related to neuromuscular irritation and include muscle stiffness, tetany and circumoral and acral paraesthesiae. Flexion of the wrist and metacarpophalangeal joints, proximal interphalangeal and distal interphalangeal joint extension and finger adduction when a blood pressure cuff is inflated to a level greater than the systolic blood pressure for 3 minutes – Trousseau's sign – is a sensitive and specific indicator of hypocalcaemia. Other symptoms of acute hypocalcaemia include neuropsychiatric effects (depression, delirium, irritability, seizures) and laryngospasm.

The clinical diagnosis can be confirmed by measuring the serum calcium level. Laboratories report calcium as both total calcium and corrected calcium. Reductions in the serum albumin level, as seen in malnutrition or nephropathy, may result in a spuriously low total calcium level although the level of unbound calcium (known as 'ionised calcium' and the biologically active form) remains

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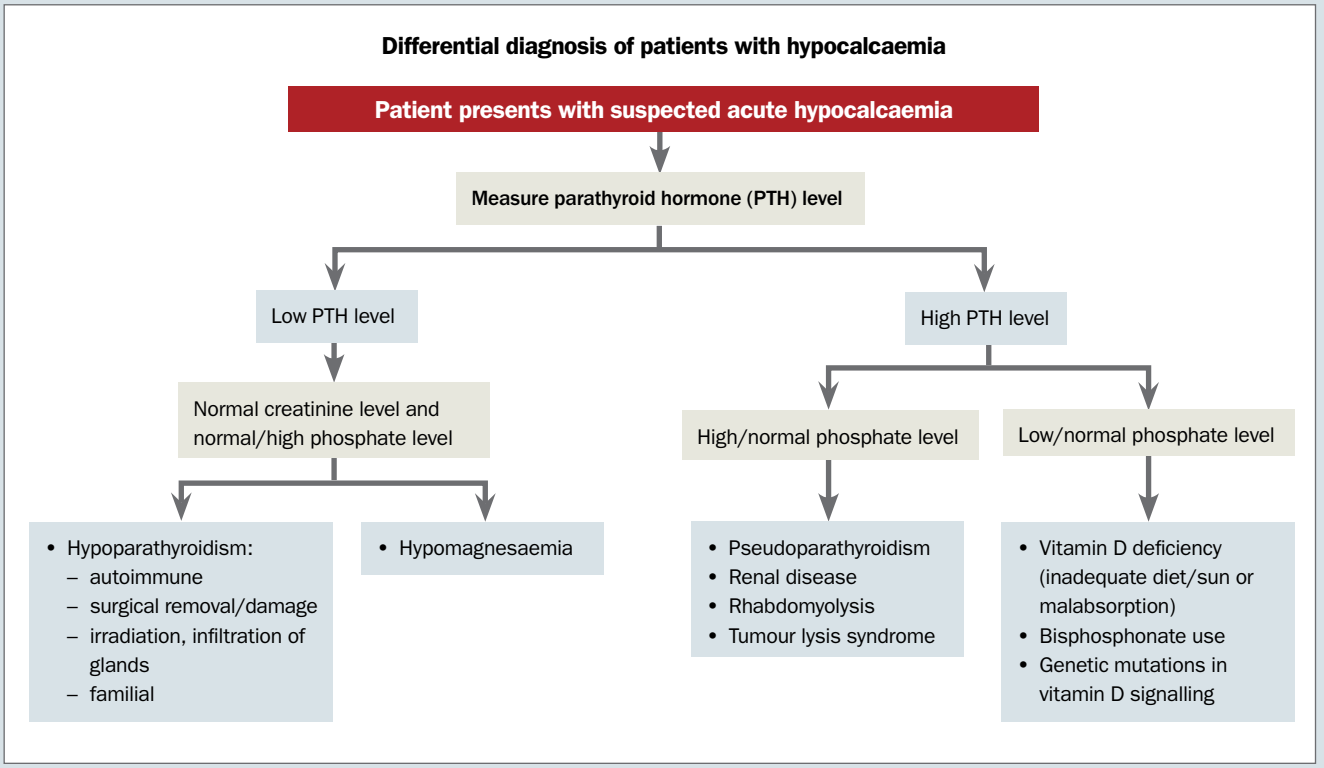

unchanged. Therefore, the calcium level may be corrected for alterations in serum albumin (then known as 'corrected calcium'). Laboratories may also directly measure unbound calcium. Ionised calcium is most often measured in patients who are critically ill and in a nonambulatory setting and in those with renal failure. In these patients, factors such as hypoalbuminaemia, acidosis and lipid infusions during parenteral nutrition lead to poor correlation between total calcium and ionised calcium levels.

Nalini's blood test results show the following results for albumin and calcium: albumin 36 g/L (reference range [RR] 36 to 47 g/L), calcium 1.8 mmol/L (RR 2.15 to 2.55 mmol/L) and corrected calcium 1.9 mmol/L (RR 2.15 to 2.55 mmol/L). These results are consistent with the clinical diagnosis of acute hypocalcaemia.

What other investigations should be performed in a person with suspected acute symptomatic hypocalcaemia?

Answer: Patients with acute severe hypocalcaemia may be at risk of life-threatening arrhythmia. An ECG is necessary to assess for prolongation of the QT interval, which indicates a risk of torsades de pointes, a potentially lethal ventricular tachycardia.

A cause for the hypocalcaemia should be sought. In cases with no obvious precipitant, basic investigations such as measuring serum levels of intact parathyroid hormone (PTH), electrolytes, urea, creatinine, magnesium, phosphate and 25-hydroxyvitamin D (25-OH vitamin D) are a good basis for working out the differential diagnosis.

Measuring the PTH level is a crucial first step in assessing the diagnostic possibilities. In the presence of a low PTH, hypocalcaemia implies hypoparathyroidism. A variety of other causes of hypocalcaemia are associated with compensatory increases in PTH, as indicated in the flowchart.

What are the common causes of acute hypocalcaemia in adults, and what is the most likely cause in this patient?

Answer: In adults, common causes of hypocalcaemia include hypoparathyroidism (most commonly postsurgical, less commonly autoimmune), renal failure, severe vitamin D deficiency, hypomagnesaemia and pancreatitis.

Hypomagnesaemia may result in hypocalcaemia by causing PTH resistance (in which case PTH levels will be raised) or, in more severe cases, by reducing PTH secretion. In these cases, hypocalcaemia will not respond adequately to calcium supplementation alone, and magnesium levels must first be corrected.

Hypocalcaemia can also be a complication of antiresorptive therapy for osteoporosis. Administration of bisphosphonates or the RANK-ligand inhibitor denosumab may precipitate hypocalcaemia. Although this is most often mild and asymptomatic, it may be severe, as in this example. Hypocalcaemia is more common after intravenous than oral bisphosphonates, and predominantly occurs after the initial dose. It occurs particularly in patients with vitamin D deficiency, chronic renal failure or hypoparathyroidism. If hypocalcaemia occurs, care should be taken before subsequent dosing, but re-administration is not contraindicated if calcium levels have normalised.

There are several rare genetic causes of

Table. The patient's blood test results

Analyte	The patient's result	Reference range
Albumin	36 g/L	36 to 47 g/L
Calcium	1.8 mmol/L	2.15 to 2.55 mmol/L
Corrected calcium	1.9 mmol/L	2.15 to 2.55 mmol/L
Urea	8 mmol/L	2.5 to 7 mmol/L
Creatinine	120 μmol/	45 to 85 μmol/L
Estimated glomerular filtration rate	36 mL/min/1.73 m^2	>90 mL/min/1.73 m^2
Magnesium	0.75 mmol/L	0.65 to 1.0 mmol/L
Phosphate	1.5 mmol/L	0.8 to 1.5 mmol/L
25-OH vitamin D	16 nmol/L	50 to 150 nmol/L
Parathyroid hormone	20.8 pmol/L	1.6 to 6.9 pmol/L

hypocalcaemia that may not manifest until adolescence or adulthood. These may result from impaired parathyroid development, action or secretion.

An ECG in Nalini reveals no QT prolongation or other abnormality. As you are concerned about this level of calcium in an elderly patient, you inform the local emergency department that you are referring Nalini for treatment.

What is the treatment for acute hypocalcaemia?

Answer: Acute symptomatic hypocalcaemia requires immediate treatment because of the risks of arrhythmia, seizure or respiratory distress due to laryngospasm. Intravenous boluses of 10% calcium gluconate (one to two ampoules; each 1 g in 10 mL) may be administered over 10 minutes. A continuous infusion of calcium gluconate at a rate of 4 g per 24 hours may be necessary if intravenous boluses do not lead to sustained improvement in calcium levels. The aim is to raise the calcium level to the low-normal range. Cardiac monitoring is recommended and infusion into a large central vein is preferred. Coexistent magnesium deficiency should also be corrected, as this may impede the therapeutic response to calcium.

Depending on the cause of hypocalcaemia, commencing treatment with oral calcitriol (1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2$ vitamin D_3], the active hormonal form) and oral calcium supplements may be necessary to maintain calcium levels once the acute deficit is corrected with intravenous calcium. Calcitriol has highly potent effects on raising the calcium level and should be used with caution because of the risks of hypercalcaemia, kidney stones and calcium deposition. Seeking specialist advice about dosing and titration is appropriate, and careful monitoring of calcium levels is advised both acutely and in the long term.

Nalini's initial biochemistry tests additional to those for albumin and calcium are shown in the Table.

How would you interpret these results? What is the most likely cause of hypocalcaemia in Nalini's case?

Answer: Nalini has stage 3 chronic kidney disease (i.e. estimated glomerular filtration rate [eGFR] 30 to 59 mL/min/1.73 m^2) and vitamin D deficiency (i.e. 25-OH vitamin D <50 nmol/L). With increasing use of anti-resorptive agents for primary and secondary fracture prevention, cases of hypocalcaemia following treatment are not infrequently described. It can occur following therapy with bisphosphonates or with the newer agent, denosumab.

Although the rate of hypocalcaemia in phase 3 clinical trials of denosumab for osteoporosis was negligible, it is important to note that patients in these trials were routinely supplemented with oral calcium and vitamin D.[1] Postmarketing data and published case series show that hypocalcaemia may occur following denosumab administration particularly in patients with severe renal impairment (those with eGFR <30 mL/min/1.73 m^2 or on dialysis, i.e. stages 4 and 5 CKD, respectively) and those with uncorrected vitamin D deficiency.[2,3] Importantly, stage 5 CKD is not an absolute contraindication to the use of denosumab. The drug is not renally excreted, so no dose adjustment is required.

Nalini's 25-OH vitamin D level was measured during her acute hospital admission nine months ago as part of the work-up for osteoporosis. At the time, the level was 30 nmol/L, and she was commenced on 1000 IU cholecalciferol and 600 mg calcium daily (the calcium in the form of calcium carbonate). Nalini spent six weeks in rehabilitation and does not recall being informed to continue this medication after her discharge home. She is dark-skinned and spends little time outdoors, especially during the winter when she struggles with the cold weather.

What are the risk factors for vitamin D deficiency and how is it defined?

Answer: Vitamin D deficiency is highly prevalent in the elderly, affecting up to half of those living in the community and in institutions. Elderly individuals are at risk of vitamin D deficiency because of age-related changes in vitamin D synthesis, reduced exposure to sunlight and malnutrition (which is common among those living in institutions).

Cholecalciferol (vitamin D_3) is synthesised in the skin on exposure to UV light. Clothing, use of sunscreen and increased skin pigmentation decrease the amount of vitamin D synthesis for equivalent sun exposure. Cholecalciferol is 25-hydroxylated in the liver, and 25-OH vitamin D_3 is the circulating form that is measurable in the serum. 25-OH vitamin D_3 is further hydroxylated to the active

form, calcitriol, in the kidney and in local organ sites.

Hypocalcaemia in renal failure is multifactorial. Reduced renal synthesis of 1,25-$(OH)_2$ vitamin D_3 due to impaired hydroxylation by 1α-hydroxylase leads to decreased intestinal absorption of calcium. Additionally, reduced phosphate excretion leads to hyperphosphataemia and increased calcium–phosphate binding, lowering levels of biologically active calcium.

Typically, vitamin D levels decline over the winter months and reach their lowest point in spring. This seasonal variation is due to reduced sun exposure in colder months and reduced UV radiation for equivalent time spent in the sun, due to the angle of the sun's rays.

There is some debate about what levels of 25-OH vitamin D should be considered sufficient. In 2011, the US Institute of Medicine recommended 25-OH vitamin D target levels of 50 nmol/L and daily vitamin D doses of 800 IU/day in older adults (over 70 years). However, the US Endocrine Society advocated a higher serum target level of 75 nmol/L and daily doses of at least 1500 to 2000 IU in this age group. Although it is generally accepted that levels below 50 nmol/L are inadequate in patients with established osteoporosis, some experts advocate higher 25-OH vitamin D targets in those with osteoporosis and would aim for levels around 75 to 100 nmol/L.

What are the options for treatment of vitamin D deficiency in patients with and without renal impairment?

Answer: In Australia, cholecalciferol is commercially available as oral tablets, capsules (1000 IU per dose) and liquids (various concentrations depending on preparation, such as 1000 IU per 0.2 mL). Lower doses of cholecalciferol may be given in combined calcium–cholecalciferol formulations. High-dose cholecalciferol (e.g. 50,000 IU in a single dose tablet) and intramuscular formulations can be made up on request by a compounding chemist.

As cholecalciferol is fat-soluble and has a long half-life, there are many options for dosing and frequency, ranging from daily tablets to once-weekly liquid preparations to monthly injections. Thus administration can be tailored to individual needs, preferences and in a manner that aids compliance. In deficient individuals, it is estimated that an intake of 1000 IU of cholecalciferol daily will increase serum 25-OH vitamin D_3 levels by approximately 25 nmol/L over a period of three months. However, the response to cholecalciferol supplementation is quite variable, depending on seasonality, other sources of vitamin D intake and genetic factors. High-dose cholecalciferol supplementation is an attractive means of increasing 25-OH vitamin D_3 levels quickly in severely deficient people, and studies have examined the safety and efficacy of single high doses ranging from 50,000 to 200,000 IU. There are, however, safety concerns with high-dose cholecalciferol therapy, with reports of vitamin D_3 toxicity, increased risk of kidney stones and a higher risk of falls and fractures in elderly subjects. Clinicians should be cautious when prescribing courses of high-dose cholecalciferol.

In people with renal impairment (stage 5 CKD), repletion of 25-OH vitamin D may not adequately correct hypocalcaemia due to impaired production of active 1,25-$(OH)_2$ vitamin D_3 from 25-OH vitamin D_3. In such cases, treatment with calcitriol may be required.

Nalini's calcium level rises to 2.1 mmol/L after intravenous calcium gluconate infusion. However, she requires ongoing intravenous dosing to maintain normal levels. She is commenced on calcitriol 0.25 µg twice daily and oral calcium carbonate 600 mg twice daily, but this is anticipated to be a short-term requirement. It is advised that she has a follow-up consultation with you three days after discharge and that the calcitriol be ceased at that point if her calcium levels are well within normal range, with ongoing close monitoring over subsequent weeks.

In the longer term, Nalini still requires repletion of her vitamin D stores. To minimise pill burden, Nalini is commenced on vitamin D drops (concentration 1000 IU/0.2 mL). Rather than use the drops daily, she is advised to add 5 mL (1 teaspoon) of the vitamin D drop preparation to a glass of milk once a week and then drink it, which equates to a dose of 25,000 IU of vitamin D per week. Her 25-OH vitamin D level is checked after three months and noted to be replete (100 nmol/L).

Another consideration is the form of the calcium supplement. Calcium carbonate requires an acid environment to dissolve whereas calcium citrate does not. Although calcium citrate is more expensive, it may be the preferred calcium supplement in Nalini's case because of her use of a proton pump inhibitor.

What is denosumab and how does it work? How long is the hypocalcaemia likely to last?

Answer: Denosumab is a humanised monoclonal antibody that inhibits RANK ligand, a substance normally made by bone cells that stimulates osteoclast maturation, activation and survival. By inhibiting RANK ligand, and thus osteoclast activity, denosumab decreases bone resorption, leading to improvements in bone mineral density and significant reduction in fracture risk. Bone resorption, however, is one of the mechanisms by which the body maintains normal calcium homeostasis. In the setting of vitamin D deficiency, compensatory rises in PTH normally stimulate osteoclastic activity, releasing calcium stored in bone into the circulation. If osteoclasts are unable to respond to PTH, this fall-back mechanism to maintain calcium levels is lost.

Denosumab may also be used in the oncological treatment of bone metastases, where a distinct 120 mg preparation is administered on a monthly basis. This dose and treatment regimen is more likely to be associated with hypocalcaemia.

The duration of denosumab-induced hypocalcaemia appears quite variable, ranging from mild transient calcium lowering to rare cases of severe prolonged hypocalcaemia following oncological treatment. These rare severe cases require calcitriol supplementation for up to six months.

Nalini's calcium levels measure 2.37 mmol/L at three days post-discharge and the calcitriol is ceased. She remains on calcium (as calcium citrate) and vitamin D replacement therapy, which she is educated

Practice points

- Acute symptomatic hypocalcaemia requires urgent treatment with intravenous calcium gluconate in a hospital setting because of the potential for serious cardiac or neurological sequelae.
- The diagnostic work up for hypocalcaemia includes measurement of renal function and levels of parathyroid hormone, 25-OH vitamin D, magnesium and phosphate.
- Hypocalcaemia can occur as a complication of any antiresorptive therapy and is more common in patients with renal impairment and/or vitamin D deficiency. The overall incidence is still low.
- Vitamin D status should be ascertained by measuring 25-OH vitamin D levels. The level should be above 50 nmol/L (or potentially 75 nmol/L) before administration of antiresorptive therapy. As 25-OH vitamin D levels follow seasonal patterns, a recent measurement is preferable.
- In vitamin D-sufficient patients, routine monitoring of calcium levels is not required.
- Calcitriol, the potent active hormonal form of vitamin D, can significantly raise calcium levels. It is often required in patients with renal impairment or hypoparathyroidism. Its use as a treatment requires careful monitoring.
- Antiresorptive medications such as bisphosphonates and denosumab offer significant fracture risk reduction. Although awareness of potential side effects is important, unwarranted fear of these complications should not preclude their use.

to take in the long term. At follow up a week later and a month later, she remains asymptomatic and her calcium levels are stable. Nalini wants to know whether she really needs treatment for her osteoporosis and if it is safe to continue with denosumab or if she should switch to another agent.

What is the safety and efficacy profile of denosumab compared with bisphosphonates? How will you advise Nalini?

Answer: Denosumab is safe to administer in the setting of renal impairment. Providing that Nalini's vitamin D levels are replete, it is unlikely that she will experience hypocalcaemia with her next injection and the treatment should not be interrupted. As this patient has previously experienced a minimal-trauma fracture, she is likely to benefit from long-term antiresorptive therapy and this would outweigh future risks posed by denosumab. Denosumab is generally well tolerated and, as stated, is a good choice for Nalini because of her renal impairment. Another option to treat her osteoporosis would be annual zoledronic acid infusions, using a renal impairment-adjusted dose. However, Nalini's experience with hypocalcaemia does not necessarily indicate that she needs to change therapy. She may continue to receive six-monthly denosumab injections and take vitamin D supplementation to ensure replete levels.

There have been concerns over the years about long-term effects of antiresorptive drugs. In 2002, concerns were raised regarding an association between bisphosphonates and osteonecrosis of the jaw (ONJ). This is a very rare side effect of bisphosphonates that particularly occurs in patients with malignancy receiving higher doses of bisphosphonates, those with poor dentition and those who smoke cigarettes. Although dentists often express concern about performing extractions in patients receiving bisphosphonates, ONJ is very rare in otherwise healthy individuals receiving standard doses of bisphosphonates or denosumab for osteoporosis

In 2010, concerns were raised regarding an association between bisphosphonates and atypical femur fractures. These unusual fractures were reported in individuals who had been receiving bisphosphonates for longer than five years, often with comorbid conditions also know to suppress bone turnover (such as inflammatory diseases and prednisone use). Atypical femur fractures are also known to occur in association with denosumab. Atypical fractures are very rare and, on balance, antiresorptive therapies prevent vastly more osteoporotic fractures. However, the occurrence of atypical fractures highlights the need to consider carefully the duration of antiresorptive therapy in individuals with osteoporosis, and to perform periodic clinical and bone mineral density assessments.

An important difference between denosumab and bisphosphonates is their duration of action. Although both therapies address osteoporosis by inhibiting bone resorption and targeting osteoclasts, denosumab is an immunomodulatory agent that suppresses bone turnover in a reversible fashion that lasts about six months. At the end of the six-month period, an increase in markers of bone turnover is seen consistent with reversal of the effect of denosumab. Therefore denosumab is only effective in the long-term when given continually at six-monthly intervals. Bisphosphonates, on the other hand, are taken up avidly by bone and induce osteoclast apoptosis (i.e. programmed cell death) in an irreversible fashion. Bisphosphonates may reside in bone and exert an antiresorptive effect for several years after their commencement.

Outcome: Nalini continued to take denosumab at six-monthly intervals and remained on adequate amounts of calcium and vitamin D supplementation. A year later, she has had no further fractures and remains asymptomatic. ET

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COMPETING INTERESTS: None.