Clinical Guideline

CALCIUM: HYPOCALCAEMIA & HYPERCALCAEMIA

SETTING Bristol Royal Hospital for Children (BRHC)

FOR STAFF Prescribers (medical and non-medical) , nursing staff and pharmacists

PATIENTS Children with abnormal calcium levels at BRHC (NB. excludes NICU patients)

OVERVIEW

When serum calcium is normal, calcium supplementation[1] is usually only required if dietary calcium intake is deficient, e.g. following lactose-free diet for cows' milk protein allergy. Dietary requirement varies with age and is relatively greater in childhood[1].

Abnormal serum calcium levels, both hypo and hypercalcaemia, can occur in children in a range of scenarios. This clinical guideline focuses on initial management: the tests you must send before treatment, to identify the cause and an outline of appropriate initial treatment. Several review articles provide background detail on differential diagnoses[2,3].

CONTENTS: Definition (page 1), Hypocalcaemia (pages 1-2), Hypercalcaemia (pages 2-3), Calcium Preparations used at BRHC(page 3), Prescribing and Administering Oral and IV Calcium Supplements (page 4-6), Monitoring (page 7), References (page 8).

DEFINITION: Normal serum adjusted calcium reference ranges[4]

Age range	**Adjusted Calcium** Reference range	**Ionised calcium** Reference range
0 - 4 weeks	2.0 - 2.7 mmol/L	1.0 – 1.35 mmol/L
4 weeks - 15 years	2.2 - 2.7 mmol/L	1.1 – 1.35 mmol/L
16 years +	2.2 - 2.6 mmol/L	1.1 – 1.3 mmol/L

HYPOCALCAEMIA (Low serum calcium)

Investigations needed: Take these if low calcium is severe (ionised calcium <0.8mmol/L) or recurrent or persists longer than 48 hours. Take these at time of low calcium. Collect first-line investigations before any oral or intravenous correction – *NOT* after:

- **Blood:** adjusted calcium, phosphate, 25-Hydroxy Vitamin D, parathyroid hormone (PTH), magnesium, alkaline phosphatase (ALP), U&E. (PTH in EDTA tube at same sampling time as when calcium low.)
- **Urine sample:** for calcium:creatinine ratio.

Once you have taken samples, then commence treatment, whilst full results awaited. PTH level only informative at time of low calcium; so send first.

Causes of Hypocalcaemia[1]

The commonest causes of hypocalcaemia are: vitamin D deficiency, hypomagnesaemia, parathyroid hormone (PTH) deficiency (complete/partial hypoparathyroidism), or PTH resistance (pseudohypoparathyroidism). Often symptomatic, but gradual onset hypocalcaemia may not show symptoms. **Newborns:** transient hypocalcaemia is common, but only in first 3 days, usually after asphyxia or respiratory distress.

Treatment of hypocalcaemia *(but first send tests on page 1)*

Mild hypocalcaemia: choose a) *or* b)

a) Treat hypocalcaemia due to vitamin D deficiency with oral calcium supplements PLUS natural vitamin D (calciferol) (see BRHC [redacted]).

b) Hypocalcaemia with low or low/normal PTH suggests complete/partial hypoparathyroidism. Treat with oral calcium supplements PLUS activated vitamin D analogue (alfacalcidol).

Severe or symptomatic hypocalcaemia: correct with [redacted] for adjusted calcium <1.6mmol/L (ionised calcium <0.8 mmol/L), also give at less severe level (adjusted calcium 1.6-2.2 mmol/L, ionised calcium 0.8-1.1mmol/L) if accompanied by the following: tetany, carpopedal spasm, stridor, seizures, QT prolongation[5].

Once infusion corrects to normal range, add in oral supplements plus specific treatment for underlying cause (see previous paragraph a) calciferol or b) alfacalcidol according to diagnostic test results).

Clinical setting for calcium infusions: Correct acute hypocalcaemia with ECG monitoring **on CED resus, PICU or HDU only.** Can give Maintenance calcium infusions on non-HDU wards.

HYPERCALCAEMIA[1] (High serum calcium)

Definition

See reference range table (page 1) for upper limit of normal. Clinically significant hypercalcaemia threshold is > 3.0 mmol/L and clinically actionable hypercalcaemia threshold > 3.5 mmol/L. Note: biochemistry phone calcium levels > 3.5 mmol/L through to requestors.

Investigations

Send tests for underlying cause before giving any corrective treatment: adjusted calcium, magnesium, parathyroid hormone (PTH, in an EDTA tube), alkaline phosphatase (ALP), 25-Hydroxy Vitamin D, U&E and collect urine for calcium:creatinine ratio.

Once first-line tests are collected, can then proceed to treatment, without awaiting full results.

Treatment of hypercalcaemia

First line: correction of dehydration with IV fluids may ameliorate hypercalcaemia – see [redacted] Drugs (e.g. thiazides and vitamin D compounds) which promote hypercalcaemia, should be discontinued and dietary calcium restricted.

Further treatment options for persisting severe hypercalcaemia (often >3.3 mmol/L) include a single zoledronic acid infusion (see [redacted]) – discuss with paediatric endocrinology team. Steroids are rarely effective but are occasionally used in sarcoidosis or vitamin D intoxication (and take several days to take effect).

Calcium Preparations used at BRHC

Medication (calcium salt)	Route of administration	Calcium content (mmol)	Notes
Calcium alliance liquid (as calcium lactate and calcium gluconate)	Oral	0.51 mmol/ml	Contains 2g fructose in 5ml. [6]
Sandocal 1000 effervescent tablets (as calcium lactate and calcium carbonate)	Oral	25 mmol per tablet	Citrus flavoured and sucrose free but contains aspartame.[6] For part doses disperse 1 tablet in 45ml water to give approximately 25mmol in 50ml. [6]
Calcium carbonate 600mg/5ml oral suspension	Oral	1.2 mmol/ml	Calcium carbonate is not the preferred calcium supplement due to poor oral absorption.[6]
Calcichew (calcium carbonate 1.25g) chewable tablets	Oral	12.5 mmol per tablet	
Calcichew D3 (colecalciferol 200 unit / calcium carbonate 1.25g) chewable tablets	Oral	12.5 mmol per tablet	Also contains vitamin D (colecalciferol)
Adcal D3 (colecalciferol 400unit / calcium carbonate 1.5g) chewable tablets	Oral	15 mmol per tablet	Also contains vitamin D (colecalciferol)
Adcal D3 caplets (colecalciferol 200unit / calcium carbonate 750mg)	Oral	6 mmol per tablet	Also contains vitamin D (colecalciferol)
Calcium gluconate 10% injection	Intravenous	0.22mmol/ml	Used for urgent [redacted] NB. irritant

Calcium chloride 14.7% injection	Intravenous	1mmol/ml	For acute hypocalcaemia associated with CPR only. NB. irritant

Prescribing and Administering Calcium Supplements

Oral Calcium [1,6]

Neonate – 4 years: 0.25 mmol/kg PO QDS*
5 – 11 years: 0.2 mmol/kg PO QDS*
12 – 17 years: 10 mmol PO QDS*

Adjust doses according to response

*Note – For long term maintenance the prescriber could consider giving total daily dose in two divided doses particularly for children of school age or to help with compliance.

Intravenous Calcium

Note extravasation risk with IV calcium – see side effects & extravasation guideline

Indication: Acute hypocalcaemia, **urgent correction** using **calcium gluconate 10%** [1,7]

Neonate: 0.11 mmol/kg (= 0.5 ml/kg of calcium gluconate 10%) over 5 -10 mins.

Children > 1 month: 0.11 mmol/kg over 5 - 10 mins (max 4.5 mmol) (= 0.5 ml/kg of calcium gluconate 10%, max 20 ml).

Electrocardiogram (ECG) monitoring needed (risk of arrhythmia if given too rapidly).

Dilute to a concentration of 0.045 mmol/mL with either sodium chloride 0.9% or glucose 5% (i.e. 1 in 5 dilution, that is, dilute each 1 mL calcium gluconate 10% with 4 mL diluent).

In emergencies, it can be given undiluted via a central venous device.

Indication: Acute hypocalcaemia, **maintenance** using **calcium gluconate 10%** [1,7]

NB. switch to oral asap due to risk of extravasation

Neonate: 0.5 mmol/kg daily over 24 hours, adjust to response. Maximum IV infusion rate for neonates 0.022mmols/kg/hr.

Children > 1 month – 17 years: 1 mmol/kg (usual max 8.8 mmol) over 24 hours via IV infusion

Maximum IV infusion Rate for children: 0.045 mmol/kg/hr (max 0.0225 mmol/min).

Dilute to a concentration of at least 0.045 mmol/mL with either sodium chloride 0.9% or glucose 5% (i.e. 1 mL of calcium gluconate with 4 mL of sodium chloride 0.9% or glucose 5 %).

Concentrations greater than 0.045 mmol/mL should be given via a central venous access device.

Indication: Acute hypocalcaemia **associated with CPR** using **calcium chloride 14.7%** [8]

All ages: slow IV injection (at least 3 minutes) 20 mg/kg (max 2000 mg) = 0.14 ml/kg (max 14 ml) with **ECG monitoring. Emergency Use**: may give neat, give via central access if possible.

Cautions

Renal impairment (risk of hypercalcaemia and renal calculi); sarcoidosis; history of nephrolithiasis; avoid calcium chloride in respiratory acidosis or respiratory failure

Glass containers[7]: Repeated or prolonged administration of calcium gluconate injection packaged in 10mL glass containers is contra-indicated in children under 18 years and in patients with renal impairment owing to the risk of aluminium accumulation; in these patients use of calcium gluconate injection packaged in plastic containers is recommended.

Side effects

Oral[1,6]

Gastrointestinal disturbances (high oral doses of calcium may cause constipation).

Intravenous:

Calcium gluconate[1,6]: bradycardia, arrhythmias, peripheral vasodilatation, cardiac depression, hypotension, nausea, vomiting, flushing, sweating, injection site reactions, severe tissue damage with extravasation – see [redacted].

Calcium chloride[9]: Too rapid intravenous injection may lead to symptoms of hypercalcaemia and may cause cardiac arrhythmias or arrest, hypotension and vasomotor collapse, sweating, hot flushes, nausea and vomiting. Other side effects include peripheral vasodilation, drowsiness, irregular heartbeat, sweating, tingling sensations, a calcium taste, a chalky taste, hypertension, venous thrombosis and bradycardia. Severe tissue damage with extravasation – see [redacted].

Compatibilities

Oral: Calcium containing preparations can affect the absorption of other medications e.g. tetracyclines, quinolones, phosphate supplementation etc. Calcium supplements should be taken at least 2 hours before or after other medicines.

Intravenous: (see also [redacted])

Disclaimer: Do not infuse with any other medicines or infusions unless compatibility has been established. Compatibilities assume medicines meet close to the vascular device. Exclusion from the incompatibility list does not imply compatibility.

Calcium gluconate[7]

Compatible: Adrenaline, aminophylline, amiodarone, calcium chloride, cisatracurium, compound sodium lactate (Hartmann's), dexmedetomidine, fentanyl, furosemide, glucose 5%, heparin, labetalol, midazolam, milrinone, noradrenaline, potassium chloride, propofol, remifentanil, sodium chloride 0.9%, sodium nitroprusside (light protected), vancomycin, vecuronium

Incompatible: oxidising agents, citrates, soluble carbonates, bicarbonates, phosphates, tartrates and sulfates (includes parenteral nutrition). Physical incompatibility has also been reported with amphotericin, ceftriaxone (see below), dobutamine hydrochloride, prochlorperazine and tetracyclines.

Calcium chloride[8]

Compatible: Compatible fluids sodium chloride 0.9%, glucose 5%.

Compatible infusions (it is assumed that medicines meet close to the vascular access device): Adrenaline, amikacin, amiodarone , calcium gluconate, chloramphenicol, dopamine, doxapram, esmolol, hydrocortisone sodium succinate, isoprenaline hydrochloride, lidocaine, micafungin, milrinone, morphine sulphate, noradrenaline, phenobarbital sodium, Plasmalyte 148, sodium nitroprusside, verapamil.

Incompatible (exclusion from the list does not imply compatibility): Amphotericin, carbonates, ceftriaxone, disodium pamidronate, dobutamine, magnesium sulfate, propofol, pantoprazole, sodium bicarbonate, sulphates, tartates, tetracyclines, thiopental sodium.

Ceftriaxone incompatibility[6]: Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term new-borns aged less than 1 month have been described. **In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites.** However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation.

Monitoring

IV administration[9]: ECG monitoring if applicable to rate, heart rate, blood pressure.

Monitor serum electrolytes, urea and bone profile including calcium and magnesium. Note use corrected/adjusted calcium level. Be aware that adjusted calcium levels are unreliable in hypoalbuminaemic patients.

If blood gases are available, ionised calcium can be monitored. Ionised calcium is more accurate than total serum calcium in patients with an abnormal serum protein (namely albumin) concentration or an acid-base balance disturbance, hence is commonly used for critically ill / high dependency patients.[10] The Gem 4000 gas machine reference range as quoted by the manufacturer is 1.15 – 1.27mmol/L. Less than 0.78mmol/L is a critically low level, more than 1.58mmol/L is a critically high level.[11]

Treatment targets: Local practice at BRHC[12] is generally to aim for ionised calcium of 1 mmol/L. In patients requiring cardiac support (e.g. those on inotropes or being treated for sepsis) the medical team may aim for a higher level of 1.2mmol/L. Targets and treatment thresholds should be decided by the medical team on an individual patient basis.

For **long term oral maintenance** therapy it is important to monitor plasma and urinary calcium.[1]

Table A

REFERENCES	1. . Paediatric Formulary Committee. *BNF for Children* (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications <http://www.medicinescomplete.com> [Accessed on 02/06/2020] 2. R Nadar, N Shaw. Investigation and management of hypocalcaemia. Arch Dis Child 399-405;105:2020. DOI: 10.1136/archdischild-2019-317482. 3. JH Davies, NJ Shaw. Investigation and management of hypercalcaemia in children. Arch Dis Child, 533-538;97:2012; DOI: 10.1136/archdischild-2011-301284 4. University Hospitals Bristol and Weston NHS Foundation trust Lab Test site available at: [redacted] [Accessed 26/05/2020] 5. Personal communication with C. Burren, 2018 – Consultant Paediatric Endocrinologist UHBW 6. Evelina Paediatric Formulary Online. Monographs: Calcium (oral supplements) (2020), Calcium Carbonate (2020), Calcium Chloride (2020). Accessed June 2020 via: http://cms.ubqo.com/public/d2595446-ce3c-47ff-9dcc-63167d9f4b80 7. Medusa injectable guide, 2019. Paediatric monograph for Calcium Gluconate [Online] version 6. Accessed via UHB intranet June 2020 8. Calcium chloride: Drug information UpToDate, 2018. Calcium chloride: Drug information (Lexicomp). Accessed via UHB intranet March 2018. 9. Medusa injectable guide, 2020. Paediatric monograph for Calcium Chloride version 6 [Online]. Accessed via UHB intranet June 2020 10. Higgins, C. 2007. Ionized calcium. Available at: https://acutecaretesting.org/en/articles/ionized-calcium [Accessed 26/05/20] 11. Personal communication with C.Pritchard, 2018 Clinical Scientist UHBW 12. Personal communication with A. Schadenberg, 2018 – Consultant Paediatric Intensivist UHBW
RELATED DOCUMENTS AND PAGES	• Extravasation And Infiltration Identification And Management In Neonates And Paediatric Patients [redacted] • Intravenous Compatibility Chart [redacted] • Fluid management in paediatric patients [redacted]
AUTHORISING BODY	Paediatric endocrine governance group
SAFETY	• IV calcium very irritant – high extravasation risk. See [redacted] • Calcium must not be administered concurrently with ceftriaxone – see [redacted] • Use calcium gluconate packaged in plastic ampoules for children (due to risk of accumulation of aluminium with glass ampoules) – see [redacted]
QUERIES AND CONTACT	• Paediatric Medicine Pharmacist, extension [redacted] bleep [redacted] • Paediatric Endocrinologist via switchboard