Zinc - ORAL

Newborn use only

2024

Alert	1 mmol Zinc = 65.4 mg.[1]
Indication	Supplementation in preterm infants <32 weeks, or <1800g Suspected/confirmed zinc deficiency
Action	Zinc is a trace element. It is important for normal growth, tissue maintenance, and wound healing.
Drug Type	Trace element
Trade Name	Bio-Logical Zinc solution – Recommended product.[2] Zincaps capsule[3] – Only if the above solution is not available.
Presentation	Bio-Logical Zinc ORAL Liquid solution: Contains 50 mg/mL of zinc sulfate heptahydrate - **equivalent to 11.3 mg/mL of elemental zinc.** Zincaps capsule: Each capsule contains 137.4 mg zinc sulfate monohydrate – **equivalent to 50 mg of elemental zinc.**
Dosage	**Dose** 2-3 mg/kg/day of **elemental** zinc[4] – Can be up to 6 mg/kg/day of **elemental** zinc (0.18-0.27 mL/kg/day of Bio-Logical Zinc solution – Prescription can be rounded off) Note: Zinc is available as salt. Dose conversion is required to determine elemental zinc. **Time of commencement (ANMF consensus)** Supplementation: any time after day 7 of life, when tolerating at least 50% enteral feed volume (Practice tip: a day after the commencement of pentavite) Suspected/confirmed zinc deficiency: As per the treating team. **Duration of treatment** Supplementation: until discharge or 42 weeks corrected gestational age. May extend to 3-6 months corrected GA. Suspected/confirmed zinc deficiency: As per the treating team. **Note:** **Dose prescribed is in addition to the intakes received from feeds/parenteral nutrition.** Parenteral (IV) recommendation of zinc is 0.4 mg/kg/day and different to oral/enteral dose.[5] Current New South Wales consensus Parenteral Nutrition formulations provide the recommended parenteral intakes. Unfortified human milk at 170mL/kg/day provides 0.7 mg/kg/day of zinc. Fortified human milk with PreNan FM85 at 170 mL/kg/day provides 2.2 mg/kg/day of zinc. Fortified human milk with Humavant+6 at 170 mL/kg/day provides 2.5 mg/kg/day of zinc.
Dose adjustment	Not applicable
Maximum dose	Supplementation: 6 mg/kg/day has been recommended by 2022 ESPGHAN consensus.[4] Higher doses may be prescribed by treating NICU teams if clinically deemed necessary.
Total cumulative dose	Not applicable.
Route	ORAL
Preparation	Bio-Logical Zinc ORAL Liquid solution: - No preparation is required. Zincaps capsule – 1. Empty one capsule into 10mL of water for injection to make a concentration of 5 mg/mL elemental zinc. 2. Shake gently to ensure even dispersion 3. Administer required dose immediately, discard any remaining solution
Administration	ORALLY or via gastric tube, preferably with feed.[6,7] Separate administration by at least 2 hours from oral doses of calcium, iron, copper and caffeine
Monitoring	May monitor plasma/serum zinc based on the feasibility for testing:[8] Zinc deficiency may be diagnosed if plasma zinc <8.4 micromol/L (55 microgram/dL). Treatment is considered adequate if plasma zinc >10.7 micromol/L (70 microgram/dL). Treatment may continue until biochemical indices are normal or growth has improved. (20)

	Note: In clinical practice, serial plasma/serum zinc concentrations may not be a reliable way to decide the titration or cessation of zinc supplementation.[9,10]
Contraindications	
Precautions	
Drug Interactions	Concomitant administration of zinc decreases the efficacy of ciprofloxacin, copper, iron and caffeine.
Adverse Reactions	Copper deficiency, nausea, vomiting, diarrhoea, hyperamylasemia.
Overdose	For further information, contact the Poisons Information Centre on 131 126 (Australia).
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Use solution prepared from capsules immediately. Discard remaining.
Storage	Store below 25°C. Protect from light
Excipients	Bio-Logical Zinc ORAL Liquid solution: hydrochloric acid, potassium sorbate, purified water.[2] Zincaps: Erythrosine, ethylcellulose, gelatin, iron oxide yellow, lactose monohydrate, macrogol 6000, magnesium stearate, maize starch, titanium dioxide.[3]
Special Comments	Diaz-Gomez et al. and Friel et al. supplemented copper in addition to zinc due to concern that zinc may suppress copper absorption.[11,12]
Evidence	**Background** After iron, zinc is the most abundant metabolically active trace element in the human body. Zinc acts as a co-factor in more than 300 metalloenzymes, through which it is involved in growth, cell differentiation, gene transcription, major pathways of metabolism, and hormone and immune function. Zinc is important for normal growth, tissue maintenance, and wound healing.[13] Zinc is absorbed throughout the small intestine and possibly the large intestine, with most occurring in the proximal gut. There is a large enterohepatic circulation of zinc. Absorption is increased by protein, amino acids, and possibly lactose and decreased by phytate (present in soy milks), calcium, iron, and magnesium. Dexamethasone impairs zinc absorption, but it is not yet clear whether this presents a clinical problem.[8] Preterm infants are at risk of zinc deficiency because 60% of zinc accretion takes place during the last trimester of pregnancy through active transplacental transfer.[8,14] **Clinical manifestations of zinc deficiency:** Symptoms/signs of zinc deficiency are nonspecific and may include poor growth, dermatitis, and low alkaline phosphatase (ALP).[15] **Subclinical zinc deficiency:** Subclinical zinc deficiency has been reported to be as high as 25% -50% in preterm infants.[16,17] Risk factors for zinc deficiency include large stool/ostomy output (e.g. short gut syndrome), thiazide diuretics (increased excretion of Zinc), and dexamethasone (impaired Zinc absorption).[20] Plasma zinc levels have low sensitivity in diagnosing Zinc deficiency as zinc is predominantly (95%) found in muscle, bone, skin and hair.[18,19] As zinc deficiency is difficult to diagnose accurately, it is better to err on the side of early Zinc supplementation.[20] However plasma Zinc level monitoring may be useful once on Zinc supplementation.[15] A recent prospective cohort study demonstrated initial rise in plasma zinc concentrations with supplementation, but subsequent drop in concentrations despite continuation of supplementation However, levels were generally >8.4 miromol/L (55 microgram/dL).[10] **Serum zinc concentrations and retinopathy of prematurity (ROP):** A prospective observational study measured serum zinc concentrations and studied its association with ROP. Serum levels <10.7 µmol/L (70 microgram/dL) was significantly associated with ROP.[21] **Serum or plasma zinc concentrations:** The use of serum or plasma zinc concentrations as a marker of zinc status is uncertain, because of the normal variations and different reference ranges. This makes it difficult to make management decisions based solely on zinc concentrations in the absence of clinical features.[8] It is reasonable to diagnose zinc deficiency when serum concentrations are less than 55 microgram/dL (8.4 micromol/L) and extra supplements could be considered in infants who have these values.[8] Concentrations greater than 70 microgram/dL appear appropriate for preterm infants. There is no guidance in the literature as to when to monitor concentrations, if at all.[8] **Efficacy** Three systematic reviews have been published since 2021. A 2021 Cochrane review in preterm infants by Staub et al included 5 trials, 3 of them from high-income countries and 2 from middle income countries.[14] Publication dates of trials ranged from 1993 to 2015. Trials used either zinc sulfate or zinc gluconate. All five trials included preterm infants

during their initial hospital admission. Four trials used dose <3 mg/kg/day, one trial used approx. 10mg/day. All trials supplemented zinc for more than 4 weeks. Review concluded that enteral supplementation of zinc in preterm infants may moderately decrease mortality (RR 0.55, 95% CI 0.31 to 0.97) and probably improve short-term weight gain and linear growth but may have little or no effect on head growth and common morbidities of prematurity. There were no data to assess the effect of zinc supplementation on long-term neurodevelopment.[14]

A 2022 systematic review by Alshaikh et al included 8 trials and found similar results. Zinc supplementation was associated with increased weight z-score, and length z-score. There was no effect on head circumference and total developmental score.[22]

A 2022 systematic review by Sinha et al included 14 trials with 9940 preterm or low birth weight infants. Enteral zinc supplementation increased weight, length and head growth and decreased diarrhea. There was no effect on mortality, acute respiratory infections, bacterial sepsis, and psychomotor development scores. The effect on mental developmental scores was inconclusive.[23]

A 2023 RCT by Sahin et al included 195 preterm infants <32 weeks. Treatment group received 12 mg/day of enteral zinc sulfate. They did not report the equivalent elemental zinc dose. Control group received 3 mg/day of zinc sulfate. Higher Zinc supplementation was found to be effective to decrease feeding intolerance, necrotising enterocolitis and late onset sepsis. No relationship between high-dose Zinc supplementation and mortality and other morbidities (hemodynamically significant patent ductus arteriosus, bronchopulmonary dysplasia, retinopathy of prematurity, and severe intraventricular haemorrhage) was observed.[24]

Timing of commencement and duration of routine supplementation: Prospective studies supplemented enteral zinc early in life, even if on partial enteral feeds and continued for at least 4 weeks and often at least until discharge or beyond.[6,11,12,24-26]

ESPGHAN 2022 recommendation for zinc supplementation: Enteral intake of 2-3 mg/kg/day is suggested, with an upper intake up to 6 mg/kg/day in some clinical circumstances.[4] It is unclear whether zinc supplementation recommended by ESPGHAN is in addition to the daily zinc intakes from feeds and parenteral nutrition.[4]

WHO 2023 recommendation for zinc supplementation: WHO Guidelines Development Group (GDG) made a conditional recommendation based on low certainty evidence that enteral zinc supplementation may be considered for human milk fed preterm or LBW infants who are not receiving zinc from another source.[27] Evidence was found for small to moderate benefits of decreased mortality (low certainty evidence), and decreased diarrhoea and increased weight, length and head circumference (moderate certainty evidence), and uncertain evidence was found of harms for mental development (low certainty evidence).[23,27] The GDG suggested that a daily dose of 1–3 mg/kg/day of elemental zinc be initiated when enteral feeds are fully established and continued until the infant receives zinc from another source.[27]

ANMF consensus: Zinc supplementation can be considered for preterm infants born <32 weeks, or <1800g at birth. Zinc supplementation can be commenced around the same time as other oral multivitamin preparation (e.g. pentavite). It can be ceased either at discharge or may continue as long as other multivitamin preparation is given, which is often up to 3-6 months of age.

Iron, copper and Zinc interactions: There are concerns regarding mutual interactions and reduced absorption among these trace elements with higher intakes of any of them.[28]

Safety

There are no reports of harm from zinc supplementation.[14] Zinc supplementation is generally safe. However, an excess of zinc (>20 mg/Kg/day) may influence absorption and retention of other trace elements such as copper and vitamin A.[15]

Pharmacokinetics

Zinc absorption is 36% of enteral Zinc intake in healthy preterm infants.[29] In a 1999 study, Zinc intake of 23 micromol/kg/day (with enteral absorption of 36% or 7 micromol/kg/day) and expected growth rates (>15 g/kg per d) were noted to absorb and retain Zinc at rates comparable to in utero accretion in healthy preterm infants.[29] However the evidence is unclear whether the suggested intake of 23 micromol/kg/day in the study can be extrapolated to sick extreme preterm infants managed in NICUs in the present day. High-phytate foods impair dietary zinc absorption, but co-ingestion of human milk may improve zinc absorption from high-phytate foods.[7]

Practice points	ESPGHAN 2022 recommendation for supplementation: Enteral intake of 2-3 mg/kg/day is suggested, with an upper intake up to 6 mg/kg/day in some clinical circumstances.[4]
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