Folic acid
Newborn use only

2024

Alert	There is no folic acid in Pentavite multivitamin liquid for infants, a commonly prescribed multivitamin used in New South Wales Neonatal Intensive Care Units and Special Care Nurseries. Human milk fortifiers contain folate and provide 44-64 microgram/kg/day of folate at 150 mL/kg/day of fortified human milk.
Indication	Prevention and treatment of folic acid deficiency including megaloblastic anaemia. Nutritional treatment of anaemia when folic acid intake may be inadequate. Supplementation following severe haemolysis – unclear evidence.
Action	Folate (Vitamin B9) is necessary for the synthesis of purines and thymine required for DNA formation. It is necessary for red cell maturation and promotion of cellular growth. The active form of folate is tetrahydrofolate. [1, 2] Supplemental folate is more bioavailable than folate normally present in food (85% versus 50%). Folinic acid is a metabolically active reduced form of folate that bypasses dihydrofolate reductase. Folate and folinic acid have a protective and probably similar effect against methotrexate related adverse effects in patients with inflammatory disease. [3, 4] As folinic acid is expensive, folic acid may be preferred.
Drug Type	B group vitamin
Trade Name	Folic acid ORAL Liquid solution prepared by pharmacy – Recommended product. Folic acid Injection Biological Therapies; Blackmores Folate Tablets; Foltabs Tablets; Megafol Tablets.
Presentation	0.05 mg/mL (50 microgram/mL) and 1 mg/mL oral liquids prepared by pharmacy – Recommended product. 5 mg/mL 1 mL vial [Biological Therapies] (each vial contains 1 mg/mL of sodium) (Not on the NSW State Formulary). 15 mg/mL 1 mL vial [Biological Therapies] (each vial contains 2.4 mg/mL of sodium.) 500 microgram Blackmores Folate, Foltabs, Megafol tablet. 5mg Megafol tablet (not appropriate for doses used in neonates).
Dose	**Enteral supplementation for very low birthweight infants*** 50 micrograms/kg/day (Recommended Daily Intake: 23-100 micrograms/kg/day)[26] **Treatment of folic acid deficiency** 100 microgram/day (**not** per kg) *Estimated enteral intakes based on 100 mL/kg human milk and 150 mL/kg fortified human milk are 8.5-16 and 44-64 microgram/kg/day respectively.[10]
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – No information. Hepatic impairment – No dose adjustment. Renal impairment – No dose adjustment.
Maximum Daily Dose	
Route	Oral

Preparation	Folic Acid Oral Liquid prepared by pharmacy – no preparation required**.** **1mg/mL solution:** Using **5 mg/mL** vial for injection (Not on NSW State Formulary) 1. Draw up 1 mL of the 5 mg/mL solution 2. Make up to 5 mL using water for injection 3. Administer required dose, discard remaining solution Using **15 mg/mL** vial for injection 1. Draw up 1 mL of the 15 mg/mL solution 2. Make up to 15 mL using water for injection 3. Administer required dose, discard remaining solution **0.05 mg/mL (50 microg/mL) solution:** Using **5 mg/mL** vial for injection (Not on NSW State Formulary) 1. Draw up 0.5 mL of the 5 mg/mL solution 2. Make up to 50 mL using water for injection 3. Administer required dose, discard remaining solution Using **15 mg/mL** vial for injection 1. Draw up 1 mL of the 15 mg/mL solution 2. Make up to 15 mL using water for injection making a 1 mg/mL solution 3. From this draw up 0.5 mL of the 1 mg/mL solution 4. Further dilute and make up to 10 mL using water for injection 5. Administer required dose, discard remaining solution **Using 500 microg tablet:** Note: This method is only to be used if pharmacy prepared oral liquid and vials for injection are not available as folic acid is not soluble in water at this volume. 1. Crush one tablet in 10mL of water for injection to make a concentration of 0.05mg/mL 2. Shake gently to ensure even dispersion 3. Administer required dose immediately, discard any remaining solution.
Administration	ORALLY or via gastric tube, with or without feed.
Monitoring	Serum folateNo specific monitoring required. Serum folate may be considered at the discretion of the treating clinician.
Contraindications	No information.
Precautions	Folic acid monotherapy is not sufficient for treatment of pernicious anaemia or other megaloblastic anaemias when vitamin B12 is deficient.
Drug Interactions	Phenytoin: Concurrent use of folic acid and phenytoin may result in decreased folate concentrations and decreased phenytoin effectiveness. Phenobarbital (phenobarbitone): Folic acid may decrease phenobarbital (phenobarbitone) concentration and its therapeutic effect; monitor phenobarbital (phenobarbitone) concentration and clinical effect. Nitrofurantoin: Concurrent use of folic acid and nitrofurantoin may result in decreased folic acid serum levels.
Adverse Reactions	Toxicity from over dosage is not reported in newborns. In preterm infants, high folate concentrations have been associated with low zinc.[5] Weight loss, neurological, gastrointestinal and psychological symptoms were also reported in adults on high doses. [6]
Overdose	No specific information.
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Use dilutions prepared from tablets and vials for injection immediately. Discard remaining.
Storage	Oral liquid prepared by pharmacy follow local instructions. Vials for injection – Store at 2°C to 8°C (Refrigerate. Do not freeze.) Protect from light. Megafol Tablets and Foltabs – Store below 30°C. Blackmores Folate – Store below 25°C

Excipients	Oral Liquid prepared by pharmacy – contact local pharmacy for more information. Blackmores Folate Tablets – contains soya bean products. Foltabs – lactose monohydrate. Megafol – crospovidone, lactose, maize starch, povidone, and magnesium stearate. Folic acid injection – disodium edetate, sodium hydroxide, and water for injections.
Special Comments	
Evidence	**Background** There is a major lack of studies to determine water soluble vitamin requirements for preterm infants. ESPGHAN 2022 proposed an intake of 23–100 µg/kg/day in preterm infants.[26] **Folate deficiency** Folate deficiency results in growth retardation, anaemia, abnormalities in neurologic status, and small intestinal morphology.[7] The haematological manifestations of folate deficiency include hyper segmentation of neutrophils, megaloblastosis, and anaemia. Serum folate levels reflect recent dietary intake, whereas red cell folate reflects longer term status. [8] **Folate Intakes** Hay et al reported the folate status in a cohort of Norwegian term breastfed infants. Folate levels remained adequate to 6 months of age, up until complementary feeds were introduced.[9] The amount of folic acid present in human milk (8.8 to 16 micrograms per 100 mL) may not be enough to meet the recommended intakes for preterm infants.[10] The use of human breast milk fortifiers or preterm formulas with higher folic acid content has been recommended for preterm infants.[11] The average folate intake from parenteral nutrition is 40 microgram/kg/day. The average concentration in feeds is fortified human milk 30 to 40 microgram/100 mL and preterm formula 35 microgram/100 mL. Oncel et al[12] reported preterm infants receiving parenteral nutrition with high folic acid content (100 microgram/100 mL) had no risk of folate deficiency up to 2 months of age. Preterm infants on fortified human milk or preterm formula also maintained serum folate concentrations. However, preterm infants fed from birth with unfortified human milk had low folate intakes, especially when mothers were smokers and/or did not receive folic acid supplementation during pregnancy. However, this study, and another by Spotswood et al, reported preterm neonates did not develop folate deficiency up to 37 weeks postmenstrual age or discharge.[12, 13] The ESPGHAN recommended intake of folic acid for preterm infants is 23 to 100 microgram/kg/day.[26] **Efficacy** ***Prevention of anaemia:*** A systematic review of folate supplementation on folate status and health outcomes in infants, children, and adolescents reported there is no evidence that additional intake of folate influences haemoglobin levels in non-anaemic paediatric patients. [8] In addition, there was insufficient evidence to determine an effect on growth. [LOE II-III; GOR C] ***Treatment of megaloblastic anaemia:*** A case series documented response to folate 60 to 480 micrograms/day intramuscularly in folate deficient infants with megaloblastic anaemia.[14] [LOE IV GOR C] ***Preterm or low birth weight infants:*** A systematic review of folate supplementation on folate status and health outcomes in infants, children, and adolescents reported limited data suggesting that supplementing the diet of low-birth-weight infants with folic acid may moderate the rapid fall of serum folate and red cell folate in the first months of life.[8] In a RCT in 141 low-birthweight infants, folic acid doses of 25, 50, and 75 micrograms/day were reported to be adequate and affect serum folate levels similarly.[15] There was no significant difference in rehospitalisation rates for transfusion although the study is underpowered. Another RCT in 184 infants born <1800 g and <36 weeks' gestation compared oral folate 100 micrograms/day for 4 months, versus 100 micrograms vitamin B12 intramuscularly monthly for 4 months versus, both supplements, or neither supplement in infants treated with iron and vitamin E.[16] Folate supplementation significantly decreased the decline in haemoglobin compared to the un-supplemented group, although the smallest decline in haemoglobin was reported in infants who received vitamin B12 alone or in combination with folate. Transfusion requirements were not reported. **Recommendation:** The current ESPGHAN recommended enteral folic acid intake for preterm infants is 23 to 100 microgram/kg/day.[26] The recent ESPGHAN/ESPEN/ESPR/CSPEN guidelines on paediatric parenteral nutrition: Vitamins recommend routine supplementation of folic acid to prevent development of folic acid deficiency in preterm infants.[17] Erythropoietin therapy for prevention and treatment of anaemia of

	prematurity may increase folic acid deficiency. Therefore, ESPGHAN has recommended combined therapy of vitamin B12 and folic acid to enhance erythropoiesis. According to the ESPGHAN 2005 Guidelines, the current recommended dose of folic acid in parenteral nutrition is 56 microgram/kg/day for infants and 140 mg/day for children. When needed as a treatment to improve erythropoiesis, the recommended dose is 23 to 100 microgram/kg/day. **Treatment of other anaemias:** ***Rhesus haemolytic disease of the newborn:*** Two reviews[18, 19] of the management of rhesus haemolytic disease reported that although administration of folic acid until 3 months of age might hypothetically decrease the need for top-up transfusions of red blood cells, current studies do not provide any evidence that administration of folic acid to infants with haemolytic disease affects the haemoglobin level[18] or reduces the need for top-up transfusions of red blood cells.[18, 19] Folic acid dosages reported in the literature vary from 25 micrograms to 5 mg/day and side effects (such as rash, fever) were uncommon. A routine supplement of folate 50 micrograms was suggested for infants with haemolytic disease of the newborn during the first three months of life.[19] ***Sickle cell anaemia:*** A systematic review found a single trial of folate 5 mg daily versus placebo in 117 children with sickle cell disease aged 6 months to 4 years and reported increased in serum folate levels but no effect on haemoglobin or symptoms of sickle cell disease. [20] [LOE II GOR C/D] ***Hereditary spherocytosis (HS):*** Megaloblastic anaemia has been reported in patients with HS. The General Haematology Task Force of the British Committee for Standards in Haematology recommend folate (2.5 mg/day up to 5 years age, and 5 mg/day thereafter) in severe and moderate HS, but probably not necessary in mild HS.[21] [LOE III/IV, GOR C] **Concurrent therapy with dihydrofolate reductase inhibitors (trimethoprim/sulfamethoxazole; pyrimethamine/sulfadiazine; methotrexate):** **Methotrexate (MTX):** Folate and folinic acid have a protective and probably similar effect against methotrexate related adverse effects (including a reduction in gastrointestinal side effects, hepatic dysfunction and discontinuation of MTX treatment for any reason) in patients with inflammatory disease.[3, 4] As folinic acid is expensive, folate may be preferred. **Pyrimethamine/sulfadiazine:** Current guidelines for treatment of the infant with congenital toxoplasmosis are for use of pyrimethamine and sulfadiazine plus folinic acid.[22,23] Folinic acid 10 mg three times a week is recommended until 1 week following cessation of pyrimethamine treatment. It was advised not to use folic acid as a substitute for folinic acid.[24] Levels of folinic acid in the CSF from folinic acid supplemented infants treated with pyrimethamine for congenital toxoplasmosis are thought to be too low to inhibit the effect of pyrimethamine.[25] However, there are no clinical trials comparing folate or folinic acid versus placebo in infants with toxoplasmosis. **Trimethoprim/sulfamethoxazole:** There are no clinical trials comparing folate or folinic acid versus placebo in infants with treated with trimethoprim/sulfamethoxazole. **Safety** Folic acid toxicity is not reported in newborns.[17] However, higher, so-called pharmacological doses may mask neurological manifestations of pernicious anaemia and may reduce the efficacy of anticonvulsant medications.[17] High folate concentrations were associated with low zinc concentrations in preterm infants.[5] Weight loss, neurological, gastrointestinal and psychological symptoms were reported in adults on high doses.[6]
Practice points	The current ESPGHAN recommended enteral folic acid intake for preterm infants is 23 to 100 microgram/kg/day.[26]
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