Vitamins in cholestasis

Newborn use only

2022

Alert	The dose recommendations for cholestasis are based on expert opinion. International units (IU) are labelled as units in this formulary. Bio-Logical Vitamin A oral solution and OsteVit D oral liquid contains sodium benzoate. Avoid exposure of >99mg/kg/day in neonates.
Indication	Neonatal cholestasis
Action	Vitamin A: Fat soluble vitamin required for vision, growth and bone development, immune function and maintenance of epithelial cells particularly in the retina and respiratory tract tissues. Vitamin D: Regulating levels of calcium and phosphorus and mineralisation of bone. Vitamin E: Antioxidant protecting cell membranes from oxidative stress. Active isomer is α-tocopherol. Vitamin K: Promotes the activation of blood coagulation Factors II, VII, IX and X in the liver.
Drug type	Fat and water soluble vitamins
Trade name	Pentavite Infant liquid 0-3 years Bio-Logical Vitamin A oral solution Ostelin Vitamin-D3 1000 IU liquid Pretorius Micel-E oral liquid Konakion MM Paediatric
Presentation	Pentavite Infant – Each 0.45 mL contains 1287 units of vitamin A and 400 units of vitamin D. Bio-Logical Vitamin A oral solution – 0.1 mL contains 2500 units of vitamin A. Ostelin Vitamin -D (Vitamin D3) oral liquid – 0.5 mL contains 1000 units of vitamin D. Pretorius Micel-E oral liquid – 0.1 mL contains 15.6 units of vitamin E. Konakion MM Paediatric – 0.2 mL contains 2 mg vitamin K_1.

Dose

Suggested starting regimen[1-4]

	Vitamin A	Vitamin D	Vitamin E	Vitamin K_1
Dose range per day (not per kg)	3000-5000 units	1000-2000 units (25-50 µg)	15-30 units	2 mg twice a week up to 2 mg daily

Medical officers to prescribe the following			Dose Range			
Vitamins	**Oral preparation** **Dose (mL) and Frequency**		**Vitamin A (units)**	**Vitamin D (units)**	**Vitamin E (units)**	**Vitamin K_1 (mg)**
Pentavite Infant	0.45 mL once or twice daily		1287-2574	400-800 (10-20 µg)	-	-
Bio-Logical Vitamin A solution	0.1 mL daily*		2500	-	-	-
Ostelin Vitamin-D oral liquid 1000 units/0.5 mL[#]	0.5 mL daily*		-	1000 (25 µg)	-	-
Pretorius Micel-E liquid	0.1-0.2 mL daily*		-	-	15.6-31.2	-
Konakion MM Paediatric	0.2 mL twice a week to daily		-	-	-	2 mg twice a week to 2 mg daily
		Total	3787-5074	1400-1800 (35-45 µg)	15.6-31.2	2 mg twice a week to 2 mg daily

*The daily dose may be administered in two divided doses.

[#]Ostelin Vitamin-D is the preferred liquid because it doesn't contain sodium benzoate. Please check the strengths in each preparation before prescribing.

Dose adjustment	Not applicable
Maximum dose	

Total cumulative dose	
Route	Oral
Preparation	No preparation is required
Administration	Administer undiluted or with a feed
Monitoring	Check serum levels of vitamins A, D, E and PT/INR in 1-3 monthly. May need more frequent monitoring in the initial weeks of therapy.
Contraindications	Hypersensitivity to vitamin A, D, E, K or any component of the formulations. Hypervitaminosis of A, E and/or D.
Precautions	
Drug interactions	May increase effects of anticoagulant and antiplatelet agents
Adverse reactions	Hypervitaminosis A: Irritability, lethargy, vomiting, bulging fontanelle. Hypervitaminosis D: Hypercalcaemia, nephrocalcinosis. Vitamin E: Potentiation of coagulopathy, sepsis, necrotising enterocolitis.
Compatibility	Not applicable
Incompatibility	Not applicable
Stability	Pentavite Infant liquid: Use within 9 weeks after opening. Other vitamins: Refer to individual product information.
Storage	All products: Store below 25°C. Protect from light. Pentavite Infant liquid: Refrigerate after opening.
Excipients	Pentavite Infant liquid: sodium saccharin, pineapple flavour. Bio-Logical Vitamin A oral solution: sodium benzoate. OsteVit-D oral liquid: sodium benzoate, caramel flavour. Pretorius Micel-E oral liquid: Potassium sorbate and soy bean products. Konakion MM Paediatric: Glycocholic acid, lecithin, sodium hydroxide, hydrochloric acid.
Special comments	Vitamin E 1 unit = 0.67 mg α-tocopherol. 1 mg of retinyl palmitate = 1818 units of vitamin A.
Evidence	**Background** There is a high prevalence of vitamin deficiency in neonatal cholestasis, with one study reporting rates of deficiency for vitamin E (71%), vitamin D (61%), vitamin A (29%) and vitamin K (13%).[3] Fat-soluble vitamin serum levels should be monitored frequently in all cholestatic infants to avoid life threatening bleeding (vitamin K deficiency), bone fractures and rickets (vitamin D deficiency), corneal/retinal defects and blindness (vitamin A deficiency), and neurologic and muscular abnormalities (vitamin E deficiency).[5] **Efficacy** Dosing recommendations for vitamins in neonatal cholestasisvary and are based on expert opinions.[1-4] Many infants will require individual supplementation of vitamins D, A, E, or K, along with the preferred multivitamin formulation.[5] Dosing recommendations for fat soluble vitamins are as follows:

Author	Vitamin A	Vitamin D	Vitamin E	Vitamin K
Feldman[4]	3000-10000 U/day	800-5000 IU/day OR 1,25 OH_2 D3: 0.05-0.2 µg/kg/day	Maintain serum targets. No dose recommendations.	2.5- 5 mg twice a week to every day
Italian society[1]	5000-25000 IU/day	800-5000 U/day	15-25 U/kg/day	2.5-5 mg twice a week to every day
King's college, London[3]	1333-5000 IU/day	1000-3000 IU/day	15-150 U/kg/day	1 mg/day
Lane et al.[2]	5000-50000 IU/day	1000-8000 IU/day	1 unit/kg/day	ORAL:2.5-5 mg IM/SQ/IV: 1-10 mg/dose

Optimal approach would be to adjust the doses based on target serum levels. Refer to practice points.

Safety

Excessive doses of vitamins can lead to adverse effects listed in adverse reactions.[1]

Practice points	Aim to maintain the normal range of serum vitamin A, E and D levels. Reference values may vary. Check with your local laboratory. Published recommendations of INR ≤1.2 is often not possible in practice despite high doses of vitamin K. Higher INR values are often accepted as long as there is no clinical evidence of coagulation dysfunction.
References	1. Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. Italian Journal of Pediatrics. 2015;41:1-12. 2. Lane E, Murray KF. Neonatal cholestasis. Pediatric Clinics. 2017;64:621-39. 3. Mancell S, Islam M, Dhawan A, Whelan K. Fat-soluble vitamin assessment, deficiency and supplementation in infants with cholestasis. Journal of Human Nutrition and Dietetics. 2022;35:273-9. 4. Feldman AG, Sokol RJ. Neonatal cholestasis. Neoreviews. 2013;14(2):e63-e73. 5. Feldman AG, Sokol RJ. Neonatal Cholestasis: Updates on Diagnostics, Therapeutics, and Prevention. NeoReviews. 2021;22:e819-e36.

VERSION/NUMBER	**DATE**
Original 1.0	21/07/2022
Current 1.0(Minor errata) **Current 1.0 (Minor errata)**	10/08/2023 28/09/2023
REVIEW	21/07/2027

Authors Contribution

Original author/s	Srinivas Bolisetty
Evidence Review	Srinivas Bolisetty, Kate Dehlsen
Expert review	Kate Dehlsen, Scott Nightingale, Michael Stormon, Usha Krishnan, Lizsa Tan, Katie Marks, Andrea Horvath
Nursing Review	Eszter Jozsa, Sarah Neale
Pharmacy Review	Mohammad Irfan Azeem, Thao Tran
ANMF Group contributors	Nilkant Phad, Bhavesh Mehta, John Sinn, Rebecca Barzegar, Kate Dehlsen, Helen Huynh, Michelle Jenkins, Stephanie Halena, Renae Gengaroli
Final editing	Thao Tran
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty