Neonatal Total Parenteral Nutrition: Clinical Implications From Recent NICE Guidelines

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Postnatal growth failure and its impact on the long term outcomes in preterm neonates is a long-standing problem. Optimal and aggressive nutrition strategies are required to ameliorate these concerns. Total parenteral nutrition (TPN) is widely practiced in management of preterm neonates. Recently published National Institute for Health and Care Excellence (NICE) guidelines provide recommendations for best practices for parenteral nutrition in neonates. However, healthcare associated sepsis, expertise as well as infrastructure of TPN, monitoring facilities and cost remain major constraints for widespread use of TPN in resource limited settings. Current update is aimed to summarize NICE and European society for Clinical Nutrition and Metabolism (ESPEN) guidelines to inform best practice for TPN for neonatologists in India.

Keywords: *Central venous access, ESPEN guidelines, Lipids.*

Preterm neonates, mostly <1500 g birthweight and/or <32 weeks gestation, are prone to subsequent growth failure. Growth failure in preterm neonates is associated with long term malnutrition and poor neurodevelopmental outcomes [1,2]. This growth failure can be ameliorated by balancing nutrition needs with optimal total parenteral nutrition (TPN) and aggressive enteral feeding [3]. Early parenteral nutrition (≤48 hours of life) in preterm neonates leads to earlier attainment of birthweight and improved weight at discharge [4]. Therefore, TPN is currently a useful strategy to achieve optimal postnatal growth, especially when enteral nutrition is compromised because of prematurity and/or underlying illnesses. Recently, National Institute for Health and Care Excellence (NICE) guidelines [5] summarized and reported available evidence systematically using the GRADE profile. NICE guidelines have recommendations on whom and when to start TPN, constituents, monitoring, and stopping TPN. Currently, there are no available national guidelines for parenteral nutrition in neonates in our country. There are wide variations in how the TPN is initiated, hiked, and monitored depending upon individual unit practices. In this update, we have summarized NICE guidelines, and compared them with European society for Clinical Nutrition and Metabolism (ESPEN), 2018 guidelines [6], to inform best practices and standardize optimal utilization of TPN (**Table I**).

Implications for Resource Limited Settings

There are specific challenges in the direct implementation of both of these guidelines in our country. The main concerns are as follows:

TPN in term/late preterm: Most of the late preterm or term neonates are managed in public sector hospitals in Special newborn care units (SNCU). Starting TPN in these units will be a challenge due to understaffing, lack of training, and infrastructure for TPN prescription.Smaller units in the private sector also face similar challenges. Evidence shows that early initiation of TPN by seven days among critically sick term neonates is associated with an increased incidence of sepsis and decreased likelihood of earlier live discharge compared to TPN initiation after day 7 of ICU stay [7]. These adverse outcomes are likely to worsen in the absence of proper asepsis and standardized practices. However, neonates in the late TPN group experienced hypoglycemia more often. Notably early and late TPN groups had similar mortality rates. Therefore, it is challenging to recommend delayed initiation of TPN in late preterm and term neonates with the available evidence.

TPN formulation (Standardized TPN): Availability and cost is a significant concern for widespread usage. In most developed countries, TPN is prepared and dispensed by trained central pharmacists. Contrastingly, TPN is

Table I Comparison of National Institute for Health and Care Excellence (NICE) guidelines with European Society for Clinical Nutrition and Metabolism (ESPEN)Guidelines for Total Parental Nutrition in Neonates

	NICE guidelines, 2020[5]	*ESPEN guidelines, 2018 [6]*	*Remarks*
Whom to start?	Immediate perinatal period: • Gestational age ≤31 wks – Start in all • 31 wk-insufficient feeds progression in first 72 h Previously established enteral feeds which was stopped due to illness: If enteral feeds are unlikely to start in 48 h (preterm neonates) or 72 h (term neonates)	Not mentioned	NICE guidelines recommend to start TPN in all neonates ≤31 wk gestational age. However, due to higher incidence of gram-negative sepsis and sepsis related countries, mortality in developing the practice of TPN should be individualized in units depending on resources.
When to start?	Start as soon as possible (preferably within 8 h).	No mention	To be initiated within 8 h of identification of an eligible neonate.
Energy	Day 1: 40-60 kcal/kg Day 2-4: gradually↑ to reach 75-120 kcal/kg/d. >Day 4: (maintenance) 75-120 kcal/kg/d.	Day 1:45-55 kcal/kg/dVLBW: Maintenance 90-120 kcal/kg/d aiming a weight gain of at least 17-20 g/kg/d after initial weight loss.	In view of limited evidence, the wide range of proposed energy intake was an expert consensus to improve consistency of care
Glucose	First 4 days: Initiate at 6- 9 g/kg/day gradually ↑9-16 g/kg/day. After 4 days of life: 9-16 g/kg/day.	Preterm neonates: Start with 5.8-11.5 g/kg/d and gradually ↑to 11.5-14.4 g/kg/d Term neonates: Start with 3.6-7.2 g/kg/d and gradually ↑to 7.2-14.4 g/kg/d	Both the guidelines recommend similarly. There is no clarity on the target range of blood glucose in both guidelines. A reasonable target range would be 100-120 mg/dL.
Amino acids	Preterm neonates First 4 days: Initiate at 1.5-2 g/kg/d, gradually ↑ to 3-4 g/kg/d. After 4 days: Give 3-4 g/kg/d Term neonates First 4 d: Initiate at 1-2 g/kg/d gradually ↑to 2.5-3 g/kg/d After 4 days: Give 2.5-3 g/kg/d.	Preterm neonates Day 1: 1.5 g/kg/d Day 2 onwards: Target 2.5-3.5 g/kg/d Term Neonates Minimum recommended intake of 1.5g/kg/d to maximum of 3g/kg/d.	The upper limit of starting dose and maximum maintenance dose of TPN should be 2 g/kg/d and 3.5 g/kg/d, respectively. For preterm neonates, formulations providing bioavailable cysteine (50-75 mg/kg/d) and taurine (>18 mg/kg/d) amino acids should be preferred [6].
Lipids	Preterm and term neonates First 4 d: Initiate at 1- 2 g/kg/d gradually ↑to 3- 4 g/kg/d. After 4 d: Give 3- 4 g/kg/d. Parenteral nutrition related liver disease:Prefer composite lipid emulsion.	Preterm and term neonates Lipid intake should not exceed 4 g/kg/d. Continuous infusion over 24 h advised. 20% lipid emulsion preferred. Unexplained thrombocytopenia needs lipid dose reduction.	Lipid lower limit (25%) and upper limit (40%) is set for avoiding hyperglycemia and hypertriglyceridemia/fatty liver, respectively.
Electrolytes	Sodium and potassium as per standard daily requirement.	In ELBW and VLBW, electrolytes can be started from day 1 after ascertaining good urine output and also considering the potential of development of non-oliguric hyperkalemia.	Sodium and potassium should ideally be started during the phase of initial weight loss in neonates i.e., from day 2-3 onwards.
TPN volume	No recommendation	Total TPN volume based on weight and day of life	ESPEN recommendations can be used to decide fluid administration.
Calcium	Preterm and term neonates Day 1-2: 3- 4 mg/kg/d Day 2 onwards: 6-8 mg/kg/d	Preterm and term (initially): 3-8 mg/kg/d; Growing preterm: 6-14 mg/kg/d	To avoid aluminium contamination in glass vials, use calcium gluconate packed in plastic container.

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	NICE guidelines, 2020[5]	*ESPEN guidelines, 2018 [6]*	*Remarks*
Phosphate	Preterm and term neonates Day 1-2: 1 mmol/kg/d and Day 3 onwards: 2 mmol/kg/d	Preterm neonates (initially): 1-2 mmol /kg/d Growing preterm:1.6-3.5 mmol/kg/d Term: 0.7-1.3 mmol/kg/d	Despite recommendation on early phosphorus, due to concern of aluminium toxicity with currently available preparations in Indian market, its use is still limited.
Iron	Preterm and term neonates No parenteral iron in first 28 d	Short term TPN (<3wk), not to give parenteral iron	-
Other trace minerals	To start as soon as TPN is started. No specific recommendation on dose	Dose recommendations given for zinc, copper, manganese, selenium, molybdenum, chromium.	Suitable preparation combining all the trace elements in appropriate dosage proportion is often not available, most lack iodine and molybdenum.
Magnesium	To give as soon as TPN is started. No specific recommendation on dose.	Preterm neonates and term (initially): 0.2- 0.5 mg/kg/d Growing preterm: 0.5-0.7 mg/kg/d	In preterm neonates, who are exposed to maternal magnesium therapy, the intake should be adapted to postnatal blood levels. Caution should be exercised in presence of acute kidney injury.
Vitamins	Start at outset as per standard requirement in lipid emulsions	Same as NICE guidelines except doses for term and preterm neonates given separately	Separate preparations of fat soluble and water-soluble vitamins tailor-made for neonates (preferred) currently not available in India.
TPN formulation	Standardized TPN formulation is preferred over individualized formulation except in babies with complex needs	Same as NICE guidelines	Availability and cost is a major concern for using standardized TPN bags in our country.
Venous access in TPN	Central venous access is preferred. Peripheral venous access - If there is anticipated short term use (<5 days) or central access is impractical.	Provides specific recommendations for central lines (type, insertion sites, ports, lumen, dressing method) and strategies for CLABSI prevention. For short-term, allows peripheral line TPN if osmolarity<900 mOsm/L	It is better not to exceed dextrose >12.5% through the peripheral line. Skin disinfection and CLABSI prevention can follow multimodal strategy as per ESPEN guidelines.
Protection from light	Advocated protection of bags, syringes and infusion sets of both aqueous and lipid solutions.	Recommended only for lipid emulsions in preterm neonates.	Most units cover only lipid solutions. Based on European Medicines Agency and Medicines and Healthcare products, Regulatory Agency guidance, all TPN solutions need to be covered.
Use of filters	No recommendation	Recommends use of filters. Membrane pore size for Lipid emulsions: 1.2-1.5 micrometer, and for Aqueous solutions: 0.22 micrometer	ESPEN recommendations are based on RCTs of pediatric patients; however, neonatal studies have not shown a clear benefit of inline filters. Therefore, routine use of inline filters cannot be currently recommended for neonatal TPN.
Stopping TPN	Neonates <28 wk: Stop once enteral feeds 140-150 mL/kg/d is attained Neonates >28 wk and fullterm: Stop	No specific neonatal recommendation	Due to higher incidence of CLABSI and cost of TPN, in Indian scenario, it can be safely

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	NICE guidelines, 2020[5]	*ESPEN guidelines, 2018 [6]*	*Remarks*
	once enteral feeds 120-140 ml/kg/d is attained		stopped once neonate starts tolerating atleast 100 mL/kg/d oral feeds

TPN: Total parenteral nutrition; CLABSI: Central line associated blood stream infection; PNALD: Parenteral nutrition associated liver disease, VKBW: Very low birthweight. No recommendation in both guidelines for acetate. Recommendations for glucose, pH, serum electrolytes, triglycerides and liver function tests monitoring are similar in both guidelines.

constituted in India by mixing the individual components by physicians and staff nurses. Manual mixing of various TPN constituents carries a risk of sepsis. There is an additional risk of errors in calculation or adding the right amount of TPN constituents with manual methods.

Micronutrients: Availability of phosphate, trace elements, and multi-vitamin solution in appropriate customized doses for neonates is a concern.

Venous access: Central line is preferred for delivery of TPN for long-term use. However, in most settings, maintenance of the central line and risk of sepsis are major limiting factors. Both guidelines allow peripheral line TPN for short-term use only.

Infections: Due to overcrowding, understaffing, and lack of laminar flow, the risk of infection is higher with TPN usage. The risk of infection can be reduced by strict asepsis during preparation and Quality improvement approaches for central line-associated bloodstream infection reduction.

Monitoring: Frequent monitoring can be a challenge, which can be overcome by using a standardized monitoring chart.

Stopping TPN: Maximal benefit of aggressive parenteral nutrition is achieved by continuing it until enteral feeds intake is above >120-140 mL/kg/day. However, to reduce the risk of sepsis-associated with central lines, TPN can be stopped once enteral nutrition delivers two-third of desired energy intake (roughly 100 mL/kg/day of oral feed).

Cost: Cost of central lines, TPN constituents, and frequent monitoring is an additional cost apart from the hospital stay for sickness and prematurity of the neonates, limiting TPN use across wider settings.

Due to the challenges mentioned above in limited-resource settings, we need to apply these guidelines cautiously in our setup. Moreover, there are no specific recommendations for TPN during cooling, volume, and infection control strategies.

In conclusion, early aggressive TPN ameliorates the risk of growth failure in premature neonates by providing calories and essential nutrients. Some of the best practices as per international guidelines may be contextual and restricted to developed nations. There is an urgent need to set up national guidelines on TPN's standardized use of TPN in neonates in India to achieve its maximum benefits.

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