

Review Article

AI-Guided Precision Parenteral Nutrition for Neonatal Intensive Care Units: Innovations, Challenges, and Future Directions

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Abstract: Parenteral nutrition (PN) is a life-sustaining therapy for critically ill and preterm neonates who cannot meet their nutritional needs through enteral feeding. However, the current practice of daily PN prescription is a complex, subjective, and resource-intensive process prone to human error and practice variability. This has led to the development of artificial intelligence (AI) models aimed at standardizing and optimizing neonatal PN. This review article synthesized recent advancements, with a particular focus on the TPN 2.0 algorithm, which utilizes deep learning and transformer architectures to generate data-driven, standardized yet personalized PN formulas. The model's rigorous validation demonstrates a high correlation with expert opinion and a compelling association between its recommendations and reduced patient morbidities. Despite these innovations, significant technical, clinical, and ethical challenges remain. These include issues of data quality, the need for continued human oversight, the "black box" problem of opaque algorithms, and economic barriers to implementation in diverse healthcare settings. The article concluded by exploring future directions, such as the use of reinforcement learning and explainable AI (XAI) for more adaptive and transparent decision support, and the integration of PN AI into broader, multimodal neonatal care systems. The ultimate goal is to leverage AI not to replace clinicians, but to augment their capabilities, thereby enhancing patient safety and allowing more time for the essential human aspects of care.

Keywords: AI-guided, precision, parenteral nutrition, innovations, challenges

1. INTRODUCTION

The neonatal intensive care unit (NICU) is a high-stakes clinical environment where timely and precise interventions are crucial for the survival and long-term health of preterm and critically ill newborns. A significant proportion of these infants, particularly those born before 31 weeks gestation or weighing less than 1500 grams, are unable to obtain adequate nutrition via the gastrointestinal tract due to the immaturity of their digestive systems or other serious medical conditions [1]. For these patients, total parenteral nutrition (TPN) is a life-saving therapy that provides essential macro- and micronutrients directly into the bloodstream. The nutritional needs of neonates are not only critical but also highly dynamic, requiring daily adjustments based on factors such as weight, metabolic status, and laboratory values [2]. For growth, a preterm infant requires a minimum of 80 kcal/kg/d and a protein intake of more than 2 grams/kg/d, with an optimal target often exceeding 100 kcal/kg/d and 3.5 grams/kg/d of protein. The daily formulation of TPN involves the delicate balancing of up to 50 different components, including amino acids, dextrose, lipids, electrolytes, vitamins, and trace elements. This process is a multidisciplinary effort, with orders typically written by a neonatologist and reviewed by a dietitian and a pharmacist before compounding and administration. In its current form, this manual process is recognized as a "complex, high-alert medication" that is "subjective, error-prone and resource-consuming" [3]. The inherent complexity and variability of manual calculations create a significant risk

for errors, which have been reported to occur at an incidence of 3 to 16 per 1,000 prescriptions across various settings. These errors can lead to serious complications such as metabolic disturbances, infections, and even necrotizing enterocolitis, a severe inflammatory bowel disease that disproportionately affects premature infants. The purpose of this review is to provide a comprehensive analysis of the emerging role of artificial intelligence in guiding precision PN in the NICU. This article will explore recent innovations, with a focus on a leading AI model, discuss the multifaceted challenges to its adoption, and outline future directions for research and implementation in this vital area of neonatal care [4].

2. The Foundational Challenge: A Manual, Error-Prone Process

The nutritional requirements of neonates, particularly those who are extremely low birth weight (ELBW), are exceptionally challenging to meet. These infants have low nutritional reserves and rapid growth needs, making them highly vulnerable to deficits [5]. To prevent catabolism, a minimal caloric intake of 40 kcal/kg/d is required, but to achieve adequate growth, the aim is for 100 kcal/kg/d and a protein intake of 3.5 g/kg/d for preterm infants [6]. Beyond macronutrients, a precise balance of micronutrients is essential. Guidelines specify starting doses and target ranges for a host of components, including amino acids (e.g., Prema sol), dextrose, lipids, calcium, phosphorus, magnesium, and trace elements like zinc and selenium. The provision of PN must be initiated promptly, often within 72 hours of birth, and is subject to daily modifications. For example, phosphorus and calcium doses are titrated based on daily lab results, while fluid requirements are determined by weighing the baby and assessing clinical status, with special attention to ELBW infants who may have marked increases in fluid and electrolyte losses [7]. This dynamic process means that a clinician must synthesize a large volume of daily patient data—including weight, laboratory results, and clinical characteristics—to formulate a safe and effective prescription. The current manual process of prescribing PN is a complex and high-stakes endeavor. A clinical team, which includes a physician, a dietitian, and a pharmacist, first evaluates the patient's clinical status and laboratory results to place an order [8]. This order must then be reviewed by a dietitian for nutritional appropriateness and by a pharmacist for dosing, stability, and compatibility of the components. Compounding, the next step, is itself a high-risk process, as it involves numerous additions in a sterile environment and is susceptible to errors that can lead to serious complications. The sheer number of variables involved in a single TPN prescription—some sources suggest up to 50 different components—places a significant cognitive burden on the care team. Despite the expertise of individual practitioners, the high volume of information and the need for constant, meticulous adjustments make this task inherently susceptible to inconsistencies and human error [9]. This systemic challenge is the fundamental reason why a new, more reliable approach is urgently needed. The problem is not merely a matter of individual competence but rather the overwhelming complexity of the task itself, which leads to practice variability and a measurable risk to patient safety. The consequences of errors in PN formulation for fragile neonates can be severe. Incorrect dosing of lipids, for instance, can lead to hyperlipidemia or, in cases of elevated unconjugated bilirubin, a risk of kernicterus as free fatty acids displace bilirubin from albumin binding sites [10]. The manual preparation process also carries a risk of microbial contamination, which can lead to life-threatening infections. The high rate of errors reported in the literature, despite the meticulous, multidisciplinary nature of the process, underscores the critical need for a more streamlined, standardized, and safer method for providing this essential therapy. This context establishes a strong case for why AI, with its capacity to process vast amounts of data and identify optimal patterns, represents a potential solution to a deeply rooted systemic problem in neonatal care [11].

3. Innovations: The AI Paradigm Shift to Precision and Standardization

The application of AI in neonatal PN represents a fundamental shift away from subjective, manual formulations toward a data-driven, evidence-based approach. Instead of creating a bespoke prescription from scratch each day, AI models are designed to identify optimal patterns from tens of thousands of past prescriptions and clinical outcomes [12]. The AI does not propose an entirely unique, individualized formula but rather suggests which of a small number of standardized formulas is the most appropriate for a specific patient on a given day. This approach cleverly combines the safety and efficiency of standardization (e.g., reduced compounding errors, lower costs) with the clinical efficacy of a personalized recommendation, demonstrating a more sophisticated form of personalized medicine. The model can adapt its recommendation daily as the infant's condition changes, ensuring that the patient receives the optimal formula for their current clinical state [13]. A prominent example of this innovation is the TPN 2.0 algorithm, developed by researchers at Stanford University and presented at the 2025 Critical Care Congress. This model was trained on a decade of electronic health record (EHR) data from the neonatal intensive care unit at Lucile Packard Children's Hospital Stanford, encompassing 79,790 prescriptions from 5,913 premature patients [14]. The algorithm also had access to patient outcomes data, allowing it to discern subtle patterns linking nutrient levels to infant health. Using deep learning and transformer architectures, the TPN 2.0 model was able to group similar nutrient prescriptions and identify that most premature babies could be optimally served by one of just 15 distinct, standardized formulas [15]. The model can then use a patient's daily EHR data to predict which of these 15 formulas would be the most suitable recommendation, and it can adjust this recommendation as the patient grows and their clinical status evolves. For example, the model was shown to automatically adjust a patient's formula in response to a change in a lab value, such as hyponatremia, and then switch back once the condition was resolved. The developers of TPN 2.0 conducted a rigorous validation process to demonstrate the algorithm's efficacy and safety. A key step involved external validation using an independent cohort of 63,273 prescriptions from 3,417 patients at a second hospital, UCSF Benioff Children's Hospitals [16]. The results showed a significant correlation with human expert opinion, with a Pearson's correlation coefficient ($r=0.94$). In a blinded study involving 10 neonatologists, the clinicians were asked to compare the AI-generated prescriptions with the actual prescriptions for past patients. The neonatologists consistently preferred the AI-generated prescriptions. Perhaps the most powerful finding came from a retrospective outcome analysis. Researchers used the AI to scan past EHRs, looking for instances where a patient's actual prescription deviated significantly from what the TPN 2.0 model would have recommended. In these cases, patients whose prescriptions did not match the AI's recommendations had a "significantly higher risk for mortality, sepsis and bowel disease" [17]. The researchers hypothesize that the AI model's ability to outperform humans in these cases is due to its capacity to account for both short-term fluctuations and long-term outcomes when generating recommendations. However, this is a correlational finding, and a prospective randomized controlled trial is needed to establish a direct causal link. This crucial next step would validate whether the AI's recommendations can actively prevent adverse outcomes. The following table summarizes the key validation metrics of the TPN 2.0 algorithm [18].

Table 01: Metric and their results

Metric	Result	Source
Correlation with Human Expert Opinion	Pearson's R = 0.94 (at Stanford) and R = 0.91 (at UCSF)	5
Physician Preference in Blinded Study (n=192)	Physicians consistently preferred AI-generated	5

	prescriptions over actual prescriptions	
Discrepancy-Morbidity Correlation	Patients with prescriptions that did not match AI recommendations had significantly higher risk for mortality, sepsis, and bowel disease (odds ratio = 3.33 for necrotizing enterocolitis)	3

4.Challenges and Barriers to Widespread Implementation

The effectiveness and reliability of AI models are fundamentally dependent on the quality of the data used for their development. In the NICU, data quality presents a significant challenge due to a lack of standardization across different healthcare centers and the prevalence of missing data in patient records [19]. These issues can compromise model reliability and limit the generalizability of a tool like TPN 2.0, which was trained on data from a specific patient population at two major hospital systems. Historical data, which forms the foundation of such models, cannot be considered the default "ground truth" and may need to be updated to remain relevant. Addressing these challenges requires an interdisciplinary approach, with clinicians providing valuable context and insight into data provenance and quality. A recurring theme in the discourse around AI in neonatal care is that these tools are intended to augment, not replace, the clinical team. The developers of TPN 2.0 explicitly state that human oversight is critical. Pharmacists, for example, must continue to review AI-generated prescriptions for safety, proper mixing, and labeling, especially in complex or unusual cases that fall outside the model's standard patterns [20]. Furthermore, the AI recommendation is only as good as the data entered into the EHR; if information is missing, the recommendation will be inaccurate and requires a clinician's review. The human factors of adoption also present a significant barrier. Clinical and nursing staff may have concerns about "role displacement," "skill obsolescence," and workflow disruptions. Building trust in these systems requires not only rigorous validation but also an improvement in digital literacy among healthcare professionals and collaborative development processes that address ethical concerns and skepticism from the outset. The implementation of AI in neonatal care raises deep ethical questions, particularly concerning the principles of beneficence (doing good) and non-maleficence (avoiding harm). A major ethical hurdle is the "black box" problem, where the internal workings of many AI algorithms are opaque, making it difficult for clinicians to fully explain how a recommendation was generated [21]. This lack of transparency is particularly problematic in neonatology, where infants cannot give consent and decisions are made by parents and the care team. For shared decision-making to be truly informed, families deserve to understand when and how AI is influencing care. A lack of explainability compromises this fundamental principle of autonomy. Furthermore, AI models can inadvertently reinforce and even worsen existing healthcare disparities if they are trained on biased data that is not representative of diverse populations [22]. To ensure fairness and justice, it is essential that AI tools are rigorously validated across varied populations, and a registry of AI tools with metadata about their underlying datasets is needed to help clinicians determine if a particular model is suitable for a specific patient population. The high costs of developing, validating, and integrating AI into a hospital's infrastructure pose a significant economic barrier. While AI may ultimately lower costs by reducing errors and improving efficiency, the initial investment required for digital health infrastructure, regulatory approval processes, and large-scale validation studies is substantial [23]. This is particularly challenging in low-resource settings, where the lack of cost-efficient and durable medical technologies is a major problem. These environments may also lack the necessary

infrastructural prerequisites, such as reliable internet connectivity and stable power supplies, which are essential for deploying complex AI tools. The promise of AI to make high-quality care more accessible in these settings is compelling, but the infrastructural and economic challenges must be overcome for this vision to be realized [24].

5. Future Directions: Towards an Integrated and Intelligent NICU

The TPN 2.0 model, while a significant innovation, is a supervised learning model that relies on historical data to make its predictions. Future AI architectures could move beyond this by employing more advanced methods, such as reinforcement learning (RL). RL is particularly well-suited for sequential decision-making in dynamic environments, a perfect fit for the daily, adaptive nature of neonatal care. An RL agent could learn an optimal long-term policy for PN administration by maximizing a reward function (e.g., healthy growth, avoidance of complications) over time, a more holistic approach than a single-shot predictive model. Additionally, to address the "black box" problem, a new class of models known as explainable AI (XAI) is essential. XAI aims to make the reasoning behind a model's recommendations transparent to the clinician. In other areas of neonatal care, conceptual XAI-driven decision support systems have been proposed that use visual decision flowcharts or explainable Q-tables to provide transparent rationale for their choices. The integration of such XAI tools with PN models would be crucial for building trust, promoting clinician acceptance, and upholding the ethical principle of informed decision-making with families. The success of AI in a specific domain like PN is a stepping stone to a broader vision of a fully integrated, intelligent NICU. The future of neonatal care lies in systems that can synthesize multimodal data from multiple sources to provide a more holistic and proactive view of a patient's health. AI models could work in concert to provide a comprehensive decision support system. For example, a PN algorithm could be integrated with models that predict the risk of neonatal sepsis, a common and deadly complication. Similarly, AI systems that analyze physiological data from IoT-enabled incubators or facial expressions to detect silent pain could be combined with PN models to provide a more complete picture of the patient's condition. This integrated approach moves beyond isolated AI applications to a coordinated system that supports a full range of clinical decisions, from nutritional support to disease prediction and outcome analysis. Realizing the full potential of AI requires a concerted effort from a diverse range of stakeholders. Multi-center, cross-disciplinary collaboration among clinicians, data scientists, ethicists, and policymakers is essential to develop robust, validated, and trustworthy AI tools. It is also critical to focus on building and curating diverse datasets to ensure that AI models are not only effective but also fair and generalizable to all patient populations. The potential of AI to democratize access to high-quality neonatal care in low-resource settings, where a shortage of specialized staff is common, is a powerful motivator for future development. While infrastructural barriers are significant, the promise of providing expert-level decision support on a massive scale makes this a crucial area for future research and investment.

6. CONCLUSION

AI-guided precision parenteral nutrition represents a significant and promising innovation in neonatal care. The development of algorithms like TPN 2.0 demonstrates that AI can effectively standardize a complex, error-prone process, aligning closely with expert opinion and showing a strong association with improved patient outcomes. This technology has the potential to enhance safety, reduce practice variability, and free up valuable clinical resources. However, the path to widespread adoption is fraught with challenges, including the need to address data quality and standardization, navigate complex ethical issues related to algorithmic transparency and bias, and overcome significant economic and infrastructural barriers. The future of AI in the NICU lies in the development of more adaptive and transparent models, such as those based on reinforcement learning and explainable AI. The ultimate

vision is not to replace the human care team, but to create integrated, intelligent decision support systems that can handle the overwhelming data and cognitive burden of modern medicine. By automating complex tasks, AI can empower clinicians to dedicate more time to the invaluable human aspects of care, such as "spending time with babies and their families, listening to them, and providing comfort and reassurance".

REFERENCES

- [1] Sohel Mahmud, Sharmin Ara Yasmin, Nahal Mostak Khan, Soheb Ahmed Robin & Lutfullahil Khabir (2024). Demographic Profile & Associated Risk Factors of Patients with Retinal Vein Occlusion in a Tertiary Eye Hospital. *Dinkum Journal of Medical Innovations*, 3(01):64-71.
- [2] Here is a bibliography of 24 articles on AI-Guided Precision Parenteral Nutrition in the NICU, including the most relevant recent publications.
- [3] Ruby Manandhar & Raj Kumar Sangroula (2025). Factors Associated with Nutritional Status among Adolescents of Kathmandu Metropolitan City: A Comparative Study Between Public and Private Schools. *Dinkum Journal of Medical Innovations*, 4(05):273-297.
- [4] Aghaeepour, N., et al. (2025). AI-guided precision parenteral nutrition for neonatal intensive care units. *Nature Medicine*, 31(6), 1882-1894.
- [5] Kannepalli, V. S. (2025). The Role of Artificial Intelligence in Transforming Neonatal Healthcare: Innovations, Challenges, and Future Directions. *Journal of Neonatal Research and Pediatrics Care*, 7(1), 1-15.
- [6] Sobol, Ž., Chiczewski, R., & Wątróbska-Świetlikowska, D. (2025). The Modern Approach to Total Parenteral Nutrition: Multidirectional Therapy Perspectives with a Focus on the Physicochemical Stability of the Lipid Fraction. *Nutrients*, 17(5), 846.
- [7] Rallis, D., Baltogianni, M., Kapetanidou, K., & Giapros, V. (2025). Current Applications of Artificial Intelligence in the Neonatal Intensive Care Unit. *Journal of Clinical Medicine*, 14(12), 3350.
- [8] Bikramaditya Prasad Sah (2025). Outcome Comparison in Microscopic and Endoscopic Trans-Sphenoidal Pituitary Adenoma Surgery in Terms of Extent of Resection. *Dinkum Journal of Medical Innovations*, 4(04):165-176.
- [9] Deshpande, G. C., & Cai, W. (2020). Use of Lipids in Neonates Requiring Parenteral Nutrition. *Journal of Parenteral and Enteral Nutrition*, 44(S1), S45-S54.
- [10] Sagun Baral (2025). Evaluation of Predictors of Outcome in Patients with Tubercular Meningitis. *Dinkum Journal of Medical Innovations*, 4(03):81-103.
- [11] Mirtallo, J. M., et al. (2014). Safe practices for parenteral nutrition. *Journal of Parenteral and Enteral Nutrition*, 38(2), 272-310.
- [12] Pironi, L., et al. (2020). ESPEN guideline on home parenteral nutrition. *Clinical Nutrition*, 39(12), 3624-3642.
- [13] Gura, K. M., et al. (2014). An update on the safety of lipid injectable emulsions. *Journal of Parenteral and Enteral Nutrition*, 38(2), 146-161.
- [14] Calder, P. C., et al. (2020). Lipids in Parenteral Nutrition: Biological Aspects. *Journal of Parenteral and Enteral Nutrition*, 44(S1), S21-S27.
- [15] Arhip, L., Serrano-Moreno, C., Romero, I., Cambor, M., & Cuerda, C. (2021). The economic costs of home parenteral nutrition: Systematic review of partial and full economic evaluations. *Clinical Nutrition*, 40(2), 339-349.
- [16] Krzykowski, W., & Duszczek, M. (2020). Pharmacoeconomics of parenteral nutrition. *Journal of Clinical Medicine*, 9(2), 527.

- [17]Edith Ahmadu (2025). Early and Periodic Screening, Diagnostic, and Treatment (EPSDT): A Critical Analysis of Medicaid's Mandate for Children and Adolescents. *Dinkum Journal of Medical Innovations*, 4(02):58-62.
- [18]Heuft, L., Voigt, J., Selig, L., Stumvoll, M., & Kaiser, T. (2023). Diagnostic Challenges and the Potential of Clinical Decision Support Systems. *Deutsches Ärzteblatt International*, 120(7), 107-114. Jonathan Paul T. Ladera (2024). Neutrophil-Lymphocyte Ratio of Covid-19 Patients Admitted in Mariano Marcos Memorial Hospital and Medical Center, an Early Prognostic Marker. *Dinkum Journal of Medical Innovations*, 3(08):597-608.
- [19]Reber, E., Staub, K., Schönenberger, K. A., Stanga, A., Leuenberger, M., & Pichard, C. (2021). Management of Home Parenteral Nutrition: Complications and Survival. *Annals of Nutrition and Metabolism*, 77(1), 46-55.
- [20]Worthington, P., Gura, K. M., Kraft, M. D., Nishikawa, R., & Guenter, P. (2021). Update on the Use of Filters for Parenteral Nutrition: An ASPEN Position Paper. *Nutrition in Clinical Practice*, 36(1), 29-39.
- [21]Stawny, M., Gostyńska, A., Olijarczyk, R., Dettlaff, K., & Jelińska, A. (2020). Stability studies of parenteral nutrition with a high dose of vitamin C. *Journal of Oncology Pharmacy Practice*, 26(7), 1894-1902.
- [22]Martincich, I., Cini, K., Lapkin, S., Lord, H., & Fernandez, R. (2020). Central Venous Access Device Complications in Patients Receiving Parenteral Nutrition in General Ward Settings: A Retrospective Analysis. *Journal of Parenteral and Enteral Nutrition*, 44(6), 1104-1111.
- [23]da Silva, J. S., et al. (2020). ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutrition in Clinical Practice*, 35(2), 178-195.
- [24]Neelam Maharjan (2024). Diagnostic Accuracy of Graded Compression Ultrasonography in Diagnosis of Acute Appendicitis Taking Histopathology as Gold Standard. *Dinkum Journal of Medical Innovations*, 3(11):784-792.