



PEDIATRIC SURGERY *Update**

Volume 64 No. 01 JANUARY 2025

Palliative Care in Pediatric Surgery

Palliative care in pediatric surgery has developed considerably over the past decade, shifting from a traditional focus on end-of-life support to a broader integration that enhances the quality of life for young patients facing complex and often life-limiting conditions. This evolution acknowledges that palliative care (PPC) in pediatrics should not be limited to terminal care but serve as an essential component throughout the continuum of a child's surgical journey, including symptom management, psychological support, and ethical decision-making.

Historically, PPC in pediatric surgery was underemphasized, partly due to the misconception that palliative care equated to giving up hope for a cure. This perception began to shift with the American Academy of Pediatrics' 2000 guidelines, which emphasized adding life to a child's years rather than simply prolonging life. Pediatric surgeons often navigate challenging ethical considerations, balancing their commitment to life-prolonging interventions with the realities of quality of life in conditions that are not always curable. Surgeons are uniquely positioned to assess whether a surgical intervention might alleviate symptoms or enhance a child's comfort. However, this often requires realistic and sensitive conversations with families who may feel conflicted between pursuing aggressive interventions and protecting their child from additional suffering.

In pediatric oncology, where palliative care has gained notable integration, PPC aims to manage both the immediate symptoms related to cancer and the lasting effects of treatment. Despite advancements in survival rates, pediatric cancer remains a leading cause of mortality beyond infancy. Many children with cancer endure significant symptom burdens, including chronic pain, fatigue, and emotional distress, which palliative care can effectively address. Studies have shown that even as survival rates improve, a significant number of survivors face debilitating long-term effects, such as organ dysfunction, cognitive impairments, and secondary malignancies. These realities position PPC not only as an end-of-life intervention but as a necessary part of the child's cancer treatment, ensuring comfort and symptom relief regardless of prognosis.

One of the critical roles that PPC plays in pediatric oncology is in symptom management. For children with advanced cancer, surgical palliative interventions often alleviate physical symptoms like bowel obstruction, respiratory distress, and severe pain, all of which significantly impact a child's quality of life. The literature highlights cases where surgical palliative interventions have reduced pain or prevented complications, such as respiratory support surgeries or procedures to relieve severe gastrointestinal symptoms. These interventions, often conducted in collaboration with palliative care teams, are part of a multidisciplinary approach where PPC aids in assessing risks, guiding parents through

options, and helping set realistic expectations about what surgery might or might not achieve.

In pediatric urology, the focus on PPC has emerged more recently. Conditions such as congenital lower urinary tract obstruction, neurogenic bladder dysfunction, and exstrophy-epispadias complex often demand repeated surgeries, intensive hospital stays, and chronic symptom management. Incorporating palliative care in pediatric urology means addressing not only the physical symptoms but also the psychosocial issues children and families face as a result of these lifelong conditions. PPC provides critical support for children undergoing complex urologic procedures, helping manage chronic pain and providing resources for families to navigate the ongoing care that often extends well into adolescence

Moreover, prenatal palliative interventions have become a significant component in maternal-fetal surgery. The availability of early diagnostics has allowed physicians to identify severe congenital conditions such as congenital diaphragmatic hernia (CDH) prenatally, providing families with the option of maternal-fetal surgery. This third option complicates traditional decision-making, which previously offered only termination or post-birth interventions. Maternal-fetal surgery exemplifies PPC's role in improving life outcomes through early, targeted interventions. The palliative care team's involvement in these cases is invaluable, guiding families through the decision-making process by weighing potential benefits and risks while considering quality-of-life outcomes for the child. PPC professionals work alongside fetal surgeons, genetic counselors, and neonatologists, providing a well-rounded approach that respects both the parents' hopes, and the practical realities associated with these surgeries.

One of the most pressing issues in pediatric surgical palliative care is timing. Surgeons and PPC physicians frequently differ in opinions on when PPC should be introduced. PPC professionals advocate for early involvement, ideally at diagnosis, to set the foundation for comprehensive, long-term care that includes symptom management and anticipatory guidance. In contrast, many surgeons only initiate PPC consultations when the child's condition deteriorates, making curative treatment unlikely. This discrepancy in timing, often attributed to cultural differences between surgical and palliative care fields, results in missed opportunities for early symptom control and comprehensive family support. Studies reveal that some surgeons delay PPC consultations out of concern that introducing palliative care too early might discourage families or imply that treatment has been exhausted.

Communication between PPC teams and pediatric surgeons is crucial for achieving optimal care outcomes. Surveys highlight that PPC professionals believe these discussions should occur much earlier in the disease process to maximize the benefits of palliative interventions. In many cases, families report that they wish they had been introduced to palliative care earlier, as it would have helped them manage their child's symptoms more effectively and provided emotional support during difficult times. For pediatric surgeons, initiating conversations about PPC can be challenging, particularly if they feel it conflicts

with families' expectations for life-saving measures. Consequently, PPC training for surgeons has emerged as a key area for improving collaboration and communication. In response, residency programs and continuing medical education increasingly include training modules focused on PPC to enhance understanding and acceptance of palliative practices among surgeons.

Research further indicates the need for multidisciplinary approaches that include PPC in pediatric surgical care. Integrating PPC professionals as core team members in surgical planning can foster an environment where families feel supported in their decisions, whether they pursue aggressive interventions or prioritize comfort and quality of life. Collaborative care allows each team member to contribute their specialized expertise—PPC professionals offer insight into symptom management and psychological support, while surgeons provide technical assessments of what surgery might accomplish. Through this collaboration, PPC ensures that surgical interventions align with family goals and the child's best interests, even when curative options are no longer viable.

Looking forward, the scope of PPC in pediatric surgery continues to expand. Conditions such as neurodegenerative disorders, complex congenital malformations, and progressive illnesses are increasingly managed with an interdisciplinary approach that includes PPC from early stages. Pediatric surgeons are recognizing the value of palliative interventions, not only for terminally ill patients but also for children with chronic, debilitating conditions. Additionally, as more pediatric surgical specialists receive PPC training, there is a greater opportunity for meaningful collaborations that can enhance the quality of life for children undergoing intensive surgical care. The evidence supports that PPC integration leads to more compassionate, well-rounded care that respects both the child's dignity and the family's experience.

In conclusion, the integration of palliative care into pediatric surgery represents a transformative shift towards a patient-centered model that prioritizes quality of life alongside medical treatment. By focusing on early symptom management, ethical decision-making, and supportive family care, PPC complements surgical interventions, ensuring that young patients with complex medical needs receive holistic, compassionate care. As PPC becomes more embedded in pediatric surgery practices, it promises to further bridge the gap between life-saving surgery and quality of life, offering families comfort, guidance, and hope in the face of challenging medical journeys.

References:

- 1- Shelton J, Jackson GP: Palliative care and pediatric surgery. *Surg Clin North Am.* 91(2):419-28, 2011
- 2- Inserra A, Narciso A, Paolantonio G, Messina R, Crocoli A: Palliative care and pediatric surgical oncology. *Semin Pediatr Surg.* 25(5):323-332, 2016
- 3- Spruit JL, Prince-Paul M. Palliative care services in pediatric oncology: *Ann Palliat Med.* 8(Suppl 1), 2019
- 4- Ott KC, Vente TM, Lautz TB, Waldman ED: Pediatric palliative care and surgery. *Ann Palliat Med.* 11(2):918-926, 2022
- 5- De Bie FR, Tate T, Antiel RM: Maternal-fetal surgery as part of pediatric palliative care. *Semin Fetal Neonatal Med.* 28(3):101440, 2023
- 6- Ellis D, Mazzola E, Wolfe J, Kelleher C: Comparing Pediatric Surgeons' and Palliative Care Pediatricians' Palliative Care Practices and Perspectives in Pediatric Surgical Patients. *J Pediatr Surg.* 59(1):37-44, 2024

7- Li O, Lee R, Boss RD, Wang MH: Palliative Care for Pediatric Urology. *J Pain Symptom Manage.* 68(1), 2024

NPO Guidelines in Pediatric Surgery

The practice of "nil per os" (NPO), or nothing by mouth, for children undergoing surgery has been a subject of intense scrutiny and evolution over the years. Various studies and guidelines highlight the balance between minimizing the risk of pulmonary aspiration during anesthesia and reducing the adverse effects of prolonged fasting on children's metabolic and psychological well-being.

Historically, the NPO protocol has been rigid, often enforcing a midnight fast for all patients scheduled for surgery. This practice, aimed at preventing aspiration, has faced criticism for its negative impact on children. Prolonged fasting can lead to dehydration, hypoglycemia, and behavioral issues like irritability and anxiety. Studies show that the current international guidelines allow more flexibility, advocating for fasting durations of 2 hours for clear liquids, 4 hours for breast milk, and 6 hours for solids. However, these guidelines are frequently exceeded in practice due to scheduling inefficiencies and miscommunication.

One of the major challenges identified is parental compliance with fasting instructions. Research indicates that less than 10% of parents fully adhere to the prescribed NPO times, with most either under-fasting or over-fasting their children. The reasons for non-compliance include inadequate understanding of instructions, fear of surgical delays or cancellations, and the difficulty of denying food or drinks to a distressed child. Miscommunication between healthcare providers and parents further exacerbates the issue, as conflicting or unclear instructions lead to confusion. Studies recommend clearer communication strategies, such as providing separate written instructions for solids and liquids and ensuring consistency in messaging.

The metabolic implications of prolonged fasting are particularly concerning for pediatric patients, as their smaller glycogen reserves make them more susceptible to hypoglycemia. This metabolic stress not only affects their energy levels but also impairs their ability to cope with the stress of surgery, potentially delaying recovery. Research highlights the benefits of shorter fasting periods, noting that children allowed to consume clear liquids up to 2 hours before surgery exhibit better hydration, reduced irritability, and lower gastric pH levels without increasing the risk of aspiration.

Recent quality improvement initiatives have shown promise in addressing the shortcomings of current NPO practices. For instance, allowing children to drink clear liquids up to 1 hour before surgery has been shown to significantly reduce fasting times and improve overall patient comfort. Such liberalized fasting guidelines align with modern evidence suggesting that aspiration risk does not increase with shorter fasting durations. These changes have been endorsed by leading anesthesia societies in Europe and Canada, emphasizing the importance of minimizing disruption to normal physiological states preoperatively.

Despite these advancements, the implementation of more liberal NPO guidelines faces resistance. Anesthesiologists and surgeons often express concerns about flexibility in scheduling and the potential for last-minute changes in surgery times. This conservatism results in a default return to the midnight fasting rule in many institutions, particularly for inpatients or cases with higher perceived aspiration risks. To counter this, some hospitals have developed task forces to standardize and enforce updated guidelines, incorporating strategies like using arrival times instead of surgery times to calculate fasting periods and encouraging the administration of clear liquids closer to the surgery.

Compliance with updated NPO guidelines also varies significantly across healthcare settings. Data show that prolonged fasting is more common in settings with less robust quality improvement frameworks or where the operational culture is resistant to change. For example, effective fasting times for clear liquids can extend beyond seven hours, even when shorter durations are recommended. Educational initiatives targeting healthcare providers and parents are critical in bridging this gap, ensuring both groups understand the rationale and safety of revised fasting protocols.

The adverse effects of prolonged fasting extend beyond the physiological to the psychological, with many children experiencing heightened anxiety and behavioral challenges due to hunger and thirst. These factors contribute to a less favorable surgical experience, both for the patient and their family. Addressing these issues requires a multifaceted approach, including better preoperative education, consistent adherence to evidence-based guidelines, and ongoing monitoring and adjustment of fasting practices based on patient outcomes.

In conclusion, while significant strides have been made in revising and liberalizing NPO guidelines for children, the practical application of these recommendations remains inconsistent. Barriers such as communication lapses, entrenched practices, and operational constraints continue to impede progress. Moving forward, greater emphasis on quality improvement initiatives, clearer communication strategies, and more flexible approaches to fasting durations are essential to enhance compliance and improve the overall surgical experience for pediatric patients. These changes must be supported by ongoing research and a willingness among healthcare providers to adopt evidence-based practices, ensuring that children receive care that is both safe and compassionate.

References:

- 1- Brunet-Wood K, Simons M, Evasiuk A, Mazurak V, Dicken B, Ridley D, Larsen B: Surgical fasting guidelines in children: Are we putting them into practice? *J Pediatr Surg.* 51(8):1298-302, 2016
- 2- Beazley B, Bulka CM, Landsman IS, Ehrenfeld JM: Demographic Predictors of NPO Violations in Elective Pediatric Surgery. *J Perianesth Nurs.* 31(1):36-40, 2016
- 3- Kafrouni H, Ojaimi RE: Preoperative Fasting Guidelines in Children: Should They Be Revised? *Case Rep Anesthesiol.* 2018:8278603, 2018
- 4- Friedrich S, Meybohm P, Kranke P: Nulla Per Os (NPO) guidelines: time to revisit? *Curr Opin Anaesthesiol.* 33(6):740-745, 2020
- 5- Singla K, Bala I, Jain D, Bharti N, Samujh R: Parents' perception and factors affecting compliance with preoperative fasting instructions in children undergoing day care surgery: A prospective observational study. *Indian J Anaesth.* 64(3):210-215, 2020

6- Schmidt AR, Fehr J, Man J, D'Souza G, Wang E, Claire R, Mendoza J: Pre-operative fasting times for clear liquids at a tertiary children's hospital; what can be improved? *Anesth Pain Med (Seoul)*. 16(3):266-272, 2021

TLR4 in Necrotizing Enterocolitis

Toll-like receptor 4 (TLR4) plays a pivotal role in the pathogenesis of necrotizing enterocolitis (NEC), a life-threatening gastrointestinal disease in premature infants. NEC is associated with a high mortality rate and severe long-term complications, including short-bowel syndrome and neurodevelopmental impairment. The role of TLR4 in NEC pathogenesis has been extensively studied, revealing its involvement in immune activation, epithelial injury, and intestinal ischemia. The following review synthesizes findings from six key studies to provide a comprehensive understanding of the molecular mechanisms underlying TLR4-mediated NEC and emerging therapeutic approaches.

NEC is primarily a disease of premature infants, occurring in up to 10% of those born with a birth weight under 1500 grams. Its pathogenesis is multifactorial, involving intestinal immaturity, dysbiotic microbiota, and exaggerated immune responses. TLR4, an innate immune receptor, has been identified as a central mediator of these processes. It recognizes lipopolysaccharides (LPS) on Gram-negative bacteria, triggering proinflammatory signaling cascades that disrupt the intestinal epithelial barrier. In premature infants, TLR4 expression is significantly elevated compared to full-term counterparts, contributing to increased susceptibility to NEC.

The role of TLR4 extends beyond its recognition of microbial pathogens. Research has shown that TLR4 activation leads to apoptosis and necroptosis of intestinal epithelial cells. These processes compromise the integrity of the gut barrier, facilitating bacterial translocation into the bloodstream and triggering systemic inflammation. TLR4-mediated necroptosis, specifically, has been highlighted as a distinct mechanism contributing to the rapid and severe tissue damage characteristic of NEC. Studies in TLR4-knockout animal models have confirmed the critical role of TLR4 in driving necroptosis, with these models demonstrating reduced epithelial injury and inflammatory responses.

Another critical mechanism by which TLR4 contributes to NEC is through its effects on the mesenteric vasculature. Activation of TLR4 on endothelial cells induces vasoconstriction and intestinal ischemia, exacerbating tissue injury. In animal models, the inhibition of TLR4 signaling has been shown to restore mesenteric perfusion and mitigate ischemic damage. This highlights the interconnected nature of inflammatory and ischemic processes in NEC pathogenesis.

The interaction between TLR4 and the enteric nervous system has also been implicated in NEC. Research has demonstrated that TLR4 activation leads to the loss of enteric glial cells, which are essential for maintaining intestinal motility and barrier integrity. The depletion of these glial cells disrupts the anti-inflammatory feedback mechanisms of the gut, further amplifying TLR4-mediated damage. The restoration of enteric glial cell function

has been proposed as a therapeutic strategy, with promising results observed in preclinical models.

One of the most consistent clinical observations in NEC is the protective effect of human breast milk. This protection is attributed to specific components of breast milk, such as human milk oligosaccharides (HMOs), which have been shown to inhibit TLR4 signaling. Studies focusing on HMOs, including 2'-fucosyllactose and 6'-sialyllactose, have demonstrated their ability to reduce TLR4-mediated inflammation and apoptosis in experimental NEC models. These oligosaccharides bind directly to TLR4, preventing its activation by LPS and other microbial ligands. Formula-fed infants, lacking these protective factors, exhibit higher rates of NEC, further underscoring the importance of breast milk in prevention strategies.

The role of the microbiome in NEC is closely linked to TLR4 activity. Premature infants with NEC exhibit a dysbiotic microbiota characterized by reduced bacterial diversity and an overrepresentation of pathogenic strains. This dysbiosis increases the availability of microbial ligands that activate TLR4, perpetuating the inflammatory cycle. Probiotic administration has emerged as a potential intervention, with several studies demonstrating that probiotics can restore microbial balance, reduce TLR4 activation, and protect against NEC. The exact mechanisms by which probiotics exert these effects are under investigation, but they likely involve competitive inhibition of pathogenic bacteria and modulation of host immune responses.

Therapeutic approaches targeting TLR4 directly have shown promise in preclinical studies. Small-molecule inhibitors of TLR4, such as specific antagonists that block LPS binding, have been effective in reducing NEC severity in animal models. These inhibitors work by attenuating the proinflammatory signaling cascades initiated by TLR4 activation, thereby preserving the integrity of the intestinal barrier. Additionally, strategies aimed at enhancing the expression of protective molecules, such as brain-derived neurotrophic factor (BDNF), have been explored. BDNF is reduced in NEC and plays a critical role in modulating TLR4 activity and maintaining intestinal homeostasis.

Another innovative approach involves the use of anti-necroptotic agents. Necrostatin-1, a specific inhibitor of necroptosis, has been shown to reduce intestinal injury and inflammation in NEC models. This therapy targets the downstream effects of TLR4 activation, preventing the catastrophic cell death and barrier dysfunction associated with necroptosis. Combined approaches that integrate TLR4 inhibition with necroptosis suppression may offer synergistic benefits.

Despite these advances, translating preclinical findings into clinical practice remains challenging. The heterogeneity of NEC, its unpredictable onset, and the limitations of current diagnostic tools complicate the development and implementation of targeted therapies. The Bell staging system, commonly used to classify NEC severity, has limitations in its ability to distinguish NEC from other neonatal gastrointestinal conditions. Improved

diagnostic criteria and biomarkers are needed to identify at-risk infants and tailor interventions effectively.

Future research should focus on elucidating the complex interplay between TLR4 signaling, the microbiome, and host factors in NEC. Advances in genomic and proteomic technologies offer opportunities to identify novel targets and refine therapeutic strategies. Additionally, the integration of precision medicine approaches, including the use of individualized probiotic formulations and personalized nutrition plans, holds promise for improving outcomes in NEC.

In conclusion, TLR4 is a central player in the pathogenesis of NEC, orchestrating a cascade of inflammatory, ischemic, and apoptotic processes that culminate in severe intestinal injury. Insights into the molecular mechanisms of TLR4-mediated NEC have paved the way for innovative therapeutic strategies, ranging from breast milk-derived interventions to targeted molecular inhibitors. While significant challenges remain, continued research into TLR4 and its role in NEC holds the potential to transform the prevention and treatment of this devastating disease, ultimately improving survival and quality of life for premature infants.

References:

- 1- Hackam DJ, Sodhi CP: Toll-Like Receptor-Mediated Intestinal Inflammatory Imbalance in the Pathogenesis of Necrotizing Enterocolitis. *Cell Mol Gastroenterol Hepatol.* 6(2):229-238.e1, 2018
- 2- Mihi B, Good M: Impact of Toll-Like Receptor 4 Signaling in Necrotizing Enterocolitis: The State of the Science. *Clin Perinatol.* 46(1):145-157, 2019
- 3- Sodhi CP, Wipf P, Yamaguchi Y, Fulton WB, Kovler M, Niño DF, Zhou Q, Banfield E, Werts AD, Ladd MR, Buck RH, Goehring KC, Prindle T Jr, Wang S, Jia H, Lu P, Hackam DJ: The human milk oligosaccharides 2'-fucosyllactose and 6'-sialyllactose protect against the development of necrotizing enterocolitis by inhibiting toll-like receptor 4 signaling. *Pediatr Res.* 89(1):91-101, 2021
- 4- Kovler ML, Gonzalez Salazar AJ, Fulton WB, Lu P, Yamaguchi Y, Zhou Q, Sampah M, Ishiyama A, Prindle T Jr, Wang S, Jia H, Wipf P, Sodhi CP, Hackam DJ: Toll-like receptor 4-mediated enteric glia loss is critical for the development of necrotizing enterocolitis. *Sci Transl Med.* 13(612):eabg3459, 2021
- 5- Liu T, Zong H, Chen X, Li S, Liu Z, Cui X, Jia G, Shi Y: Toll-like receptor 4-mediated necroptosis in the development of necrotizing enterocolitis. *Pediatr Res.* 91(1):73-82, 2022
- 6- Duess JW, Sampah ME, Lopez CM, Tsuboi K, Scheese DJ, Sodhi CP, Hackam DJ: Necrotizing enterocolitis, gut microbes, and sepsis. *Gut Microbes.* 15(1):2221470, 2023

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* PSU 1993-2025
ISSN 1089-7739

