Published in final edited form as:
J Child Neurol. 2021 October ; 36(12): 1120–1127. doi:10.1177/08830738211045238.

Neuropalliative Care for Neonates

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Abstract

Many childhood neurologic conditions are first diagnosed in the perinatal period and shorten or seriously alter the lives of affected infants. Neonatal neuropalliative care incorporates core practices and teachings of both neurology and palliative care and is directed toward patients and families affected by serious neurologic conditions in the antenatal and immediate newborn period. This review outlines key considerations for neurologists hoping to provide a neuropalliative care approach antenatally, in the neonatal intensive care unit, and around hospital discharge. We explore 4 core domains of neuropalliative care: (1) family-centered communication, (2) prognostication, (3) decision making, and (4) pain and symptom management. We address special considerations in care at the end of life and in varied cultural and practice contexts.

Keywords

neonate; quality of life; infant; preterm; pediatric

Introduction

Many serious childhood neurologic conditions are first diagnosed in the fetal, perinatal, or immediate postnatal period (Table 1). Evolving diagnostic modalities have enabled early recognition of neurologic disorders, underscoring the need for early dedicated fetal and neonatal neurologic care. As the lives of infants with neurologic conditions are often

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Author Contributions
Dr. Sharla Rent conceptualized the review, participated in drafting the original manuscript, provided revisions, and approved the final draft of the manuscript. Dr. Margarita Bidegain provided expert content review, provided revisions, and approved the final draft of the manuscript. Margaret Bost participated in drafting the original manuscript, provided revisions, and approved the final draft of the manuscript. Dr. Chi Hornik provided expert content review, provided revisions, and approved the final draft of the manuscript. Dr. Monica Lemmon provided expert content review, provided revisions, and approved the final draft of the manuscript.

Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MEL has received compensation for medicolegal work. Other authors report no conflict of interest.

shortened or seriously altered by their diagnoses, they require tailored support that bridges the core practices and teachings of both neurology and palliative care.

Neuropalliative care "focuses on the specific needs of patients with neurologic illness and their families, including both primary and specialist palliative care."[1] The neuropalliative care specialty applies core palliative care principles, such as effective communication, partnership between families and the medical team, shared decision making, and pain and symptom management, to infants with serious neurologic conditions. Although dedicated palliative care teams often consist of physicians, nurses, social workers, psychologists, chaplains, and others,[2] neuropalliative care is best thought of as a way of providing care rather than a classification of certain team members. Regardless of their stage of training, neurologists can provide added benefit to their patients by being able to integrate palliative care principles in the management of serious neurologic conditions.[3]

Neuropalliative care offers an extra layer of support to both families of infants with neurologic conditions and members of the care team. Although all clinicians can apply palliative care principles to their practices, providers with advanced training in palliative care can facilitate difficult conversations, promote shared decision making, and manage pain and other distressing symptoms. Additionally, tailored palliative care teams can recognize and manage moral distress experienced by other members of the patient care team.[4] Given these benefits, initiation of palliative care is appropriate as soon as a serious neurologic condition is diagnosed, even in cases with prognostic uncertainty.[2,5] As technological advances have led to prompt diagnosis of serious neurologic conditions, it is often possible, and encouraged, for neuropalliative care to be initiated prior to birth. Early contact between neuropalliative care clinicians and families allows for the establishment of a trusting relationship that may span an infant's clinical course and form the basis for future interactions between the family and health care team.

A recent statement on priorities to move neuropalliative care forward identified 9 core palliative care skills for neurologists: identify common palliative care needs associated with specific neurologic disorders, acquire communication skills including empathetic listening, effectively estimate and communicate prognosis and uncertainty, master shared decision making and support for common preference-sensitive decisions and choices, recognize and manage caregiver distress and needs, provide basic psychosocial and spiritual support, detect and manage different types of pain, and be aware of palliative care options of last resort.[1] A formal consensus statement similarly recognized the benefit of early integration of palliative care, the use of a multidisciplinary team, clear communication with families, and education for professionals involved in the care of patients with progressive or devastating neurologic disease.[6]

In this review, we explore these skills within the framework of 4 core domains of neuropalliative care: (1) family-centered communication, (2) prognostication, (3) decision making, and (4) pain and symptom management. We will address these domains across the patient care trajectory, from antenatal to discharge.

Family-Centered Communication

Infants with neurologic injury are typically cared for by multiple clinicians, including neonatologists, obstetricians, neurologists, palliative care clinicians, geneticists, therapists, and surgeons. Given the sheer number of clinicians involved in an infant's care, timely and accurate communication between team members and families is both challenging and essential. Existing data suggest that lack of consensus among teams is a source of parent distress[7] and, paradoxically, that parents of infants with neurologic conditions may feel progressively less informed throughout the course of a prolonged hospitalization,[8] reinforcing the importance of regular communication. Regular interdisciplinary team meetings can help promote consistent communication. Such meetings may include the patient's primary nurse, social work, members of the primary team, and relevant subspecialists. For many families, spirituality is central to their processing of the neonatal intensive care unit experience. Some families may find it helpful to include a spiritual counselor in major conversations with the clinical team. This communication must be empathetic and personalized, as families are often at different stages in their ability to receive and process complex information.

Family culture, religion, and personal beliefs may also affect how families approach difficult conversations and neuropalliative care decisions.[9] Families of neurologically complex children come from a diverse range of cultural, ethnic, and spiritual backgrounds. Family-centered palliative care can ensure that a family's beliefs and associated goals of care are honored. Individual families may also have personal preferences regarding the care of their child separate from their larger belief system, and it is important for medical staff not to assume a family's requests or reactions to be strictly culture based.[5] Similarly, individual families who identify with a given culture or religion may not necessarily ascribe to the predominant belief patterns of that group. Each family should be approached as individuals navigating their way through making challenging decisions regarding their infant's care.

Prior work has suggested used the AMEN tool to negotiate conversations, which encourages clinicians to (1) *affirm* the patient's belief, (2) *meet* the family where they are, (3) *educate* from their role as a clinician, and (4) assure the family of their commitment, *no matter what*.[10] In cases where prognosis is poor or the family maintains "hope for a miracle," approaching conversations with families from a place of collaboration may enable families to be open about their wishes. Another approach to communicate medical information amid uncertainty includes addressing "what-if" scenarios, allowing the medical team and the family to talk through potential future scenarios that are especially worrisome to the family.[11] Such conversations may allow a family to feel heard, be open about their beliefs, and share their worries with their medical team. Using either of these approaches, or others, may help clinicians provide better care to their patients.

Antenatal Counseling

For many families, a neuropalliative care approach can be initiated in the antenatal period. Antenatal counseling is especially important in cases where the infant is unlikely to survive much beyond delivery or the infant has a congenital condition associated with significant neurologic impairment.[12] A small but increasing number of women are choosing to continue pregnancy in cases of known severe fetal anomalies[13,14]; however, only a minority of pregnant women whose fetuses have “uncertain, likely poor” or “nonsurvivable” conditions receive prenatal palliative counseling.[15] Families of fetuses with serious congenital anomalies evaluated by neonatology and who additionally receive antenatal palliative care consultation are more likely to choose a noncurative care plan rather than aggressive therapy, when compared to those without palliative care consultation.[16]

The goals of antenatal neuropalliative care are to establish a clinician-patient relationship, engage in shared goal setting for the fetus, and introduce palliative care concepts early as part of the care plan. A clear description of the role of palliative care, including maximizing infant quality of life, management of pain and distress, and multidisciplinary family support, may increase a family’s receptiveness to these interventions after delivery. Establishing a palliative care birth plan may provide some families with a sense of control.[5] Clear documentation of the birth plan can promote consistency between the prenatal and postnatal care teams.[17] When approaching these conversations, it is important to realize that parents may have varied levels of medical knowledge about their infant’s neurologic condition, even between couples.

In the Neonatal Intensive Care Unit

The first hours after birth can be an incredibly tumultuous time for families. In cases in which a diagnosis was known during pregnancy, an infant’s clinical status can still vary significantly from what was anticipated prenatally. For many infants and families, a neurologic diagnosis is not known until delivery or after birth. In hypoxic ischemic encephalopathy, for example, pregnancy is often uncomplicated until an obstetric concern arises that results in an urgent delivery. Parents of infants with hypoxic ischemic encephalopathy may go through a traumatic and unexpected loss of the typical birth experience, which may be amplified by fragmented communication.[18] For both anticipated and expected cases of newborn neurologic injury, health care teams can consider a family conference including relevant subspeciality clinicians within the first 72 hours after neonatal intensive care unit admission to ensure that families are informed about the potentially complex or unexpected clinical status of their child.[19] Ongoing conversations about goals of care are essential and may take the form of both scheduled check-ins for routine updates on an infant’s clinical course as well as family meetings at critical decision points. Engaging families in daily rounds is a common and effective way to improve communication and reduce the risk of inconsistent information from different team members.

Clinicians should be aware of several common barriers to effective communication in the neonatal intensive care unit. A family’s understanding of their infant’s condition may vary depending on their baseline medical knowledge, what information they have received previously, anxiety, and past experiences with loss.[5] Clinicians can assess parent understanding, and revisit previously shared information if relevant. Additionally, families and clinicians may focus on different key issues when discussing prognosis and goals of care; clinicians are more likely to focus on neurodevelopmental outcomes, whereas parents are more likely to be concerned about survival.[20] Eliciting family members’ concerns and values during goals of care conversations will allow clinicians to more effectively partner with parents, or guardians, and aim for what matters to them. Clinicians often share medical information with only 1 family member, placing a burden on them to communicate clinical information to the rest of the family.[18] It is important for clinicians to strive to include key family members and support people in recurring care meetings to alleviate this burden. Logistical barriers to effective communication may also exist, including parents or guardians who are unable to frequently be present at the infant's bedside. In such situations, it is important for the care team to communicate daily with the family, keeping them abreast of the infant's day-to-day clinical status. Video or telephone conferencing with the larger care team can be considered with any major change in clinical status or before any major procedures. Lastly, clinical providers can work in tandem with hospital social workers to identify and try to eliminate existing barriers to parents being present in the neonatal intensive care unit.

Further etiquette for effective communication from families of infants in the neonatal intensive care unit include team members introducing themselves and their role, addressing infants by the family's preferred name rather than diagnosis, adjusting language and information to meet family preferences, and acknowledging family members' roles in caring for their loved one.[21] It is worth noting that many families feel that the bedside nurse, who is often longitudinally involved in their infant's care, is their primary source of information.[18] This highlights both the importance of including nursing in care meetings and the benefit of longitudinal relationships in an environment in which other clinicians rotate on and off the unit. Neurology teams can consider a longitudinal attending model to enhance continuity with the families of infants with neurologic conditions in the neonatal intensive care unit.

Approaching Discharge

At the time of discharge, clinicians may focus conversations about an infant's care on resolving any remaining questions or concerns, readying parents, or guardians, to take an active caretaker role, elucidating parental goals for after discharge, and solidifying plans for outpatient follow-up. Parents may have concerns related to caring for their child, how their child will fit in with older siblings, balancing caretaking with employment, and financial strain.[7] Contingency planning for some families will depend on whether their primary goal is for their child to have as long a life as possible or for their child to spend more time with family and avoid repeat trips to the hospital. Coordination of follow-up care with local multidisciplinary high-risk infant clinics and/or pediatric palliative/hospice services is essential at discharge. Teams can prioritize making follow-up appointments prior to discharge, to reduce the burden of scheduling on families. If this is not possible, teams can provide families with clear instructions on how to schedule the necessary follow-up care for their child and assist in arranging these appointments. Given the high potential for ongoing care needs following discharge, neurologists are uniquely positioned to remain involved in an infant's care longitudinally. As many families' goals will evolve as their child grows, it is critical for neurologists to revisit key clinical information and goals of care in follow-up visits.

Prognostication

Prognostic uncertainty exists for many infants with neurologic conditions due to unknown timing or cause of neurologic injury, the lack of a definitive biomarker for injury severity,[22] and the difficulty of translating population-level estimates into individual risk.[23] Infants' clinical examinations often evolve over time, making it a challenge to predict outcomes based on a single physical examination.[24] Waiting for a clear clinical picture to emerge is often impractical. Many cases of neurologic injury have uncertain timelines, with clinical symptoms potentially presenting over a wide time period. Clinicians can proactively incorporate a neuropalliative care approach into the care of infants, thereby providing more holistic care for the child and adding an extra layer of support for families and clinicians.[2] This approach might involve normalizing prognostic uncertainty, being open about the limitations of diagnostic tests, and helping families manage the effects of uncertainty on their ability to live in the present.[23] Clinicians who frequently discuss neurologic prognosis with families can assess their communication practices by focusing on the principles of reflection, humility, open-mindedness, partnership, and engagement.[25,26]

Antenatal Diagnoses

Neurologic diagnoses often become apparent at the fetal anatomy screen between 18 and 22 weeks' gestation.[27] Common conditions that can be identified via prenatal imaging include brain and spine malformations and antenatal brain injury. These diagnoses can be further characterized with prenatal magnetic resonance imaging (MRI) and genetic screening, which can include cell-free DNA testing, chorionic villus sampling, and/or amniocentesis.[28,29] Information about diagnosis and prognosis may guide families as they approach high-stakes decisions in the antenatal period. Such decisions might include further genetic screening or diagnosis, consultation with other specialists such as neurosurgery, birth location, intensive care interventions, or limitations of resuscitation. In these cases, neurologists with training in fetal neurology can help patients by communicating key information about prognosis and prognostic uncertainty. When possible, these conversations should include members of the neonatology team and perinatal palliative care clinicians.

In the Neonatal Intensive Care Unit

Prognostication in the neonatal intensive care unit can be informed by clinical evaluations and a variety of diagnostic tests. Common conditions diagnosed at birth or in the neonatal intensive care unit include hypoxic ischemic encephalopathy, perinatal arterial ischemic stroke, neuromuscular conditions, inborn errors of metabolism, intraventricular hemorrhage, and periventricular leukomalacia. Brain imaging, electroencephalo-graphic (EEG) background, and infant examinations are key sources of data used to guide prognostication. For neurologic conditions concerning for an underlying genetic anomaly, genetic testing is increasingly available to families. Despite the increasing yield of genetic testing, results are often inconclusive, lead to a diagnosis with unclear prognosis, or, in some settings, have turnaround times that are prohibitive to inclusion in real-time decision making.[2] Previous work has found that uncertainty about long-term outcomes is a source of both acute and long-term distress for families of children with neonatal seizures and hypoxic ischemic encephalopathy.[7,30] Clinicians can decrease distress about uncertainty by discussing what outcomes are possible using a best case, worst case, and most likely approach.[31]

Approaching Discharge

Prognostic uncertainty remains a cause of distress for families after discharge, with many parents experiencing recurrent grief as their children do not meet developmental milestones.[30] Many families leave the neonatal intensive care unit with unanswered questions and/or unmet communication needs. Prior to discharge, families benefit from meeting proactively with the medical team to review the neonatal course, discuss prognosis, and establish a follow-up plan. Although prognostic uncertainty is inherent to neonatal neurology care, an infant's developmental trajectory typically becomes increasingly clear over time. Neurologists should revisit prognosis in follow-up clinic as prognostic uncertainty decreases.

Decision Making

For infants with complex neurologic conditions, a shared decision-making approach is preferred for preference-sensitive decisions.[16,32] A neuropalliative care approach to these decisions includes helping families understand prognosis, envision life after discharge, and clarify their values. Previous work has shown that families often prioritize religious or spiritual beliefs rather than morbidity or mortality predictions when making high-stakes decisions.[33] Therefore, a multidisciplinary approach that includes neurologists, neonatologists, palliative care clinicians, chaplains, and social workers is helpful in ensuring that family values and preferences are honored in all decisions made.[34]

Decisions Made Antenatally, in the Neonatal Intensive Care Unit, and Around Discharge

High-stakes decisions are made throughout an infant's clinical course. In the antenatal period, shared decision making focuses on development of a birth plan for infants with life-limiting or life-altering neurologic conditions. Such a plan will often include the location of birth as well as resuscitation measures. Some antenatal decision making will require balancing fetal and maternal risks. For example, fetal repair of myelomeningocele can be accompanied with increased risk of maternal complications.[35] In the neonatal intensive care unit, parents and guardians are faced with a variety of complex decisions including intensive care interventions and choices related to surgical procedures. Of note, pursuing some standard of care treatments, such as therapeutic hypothermia in the setting of hypoxic ischemic encephalopathy, may be viewed as a choice by families.[7,36] As infants approach discharge, a shared decision-making approach can help families make choices about home health services, discharge with hospice care or discharge to an inpatient long-term care facility. After discharge, families may face decisions regarding readmission to the hospital, the need for additional therapeutic or surgical procedures, or limitations of resuscitation. Neurologists will often follow patients longitudinally and should be aware of shifting and evolving family's goals as parents learn more about caring for their child with significant medical needs and infants develop relationships with their families and communities.

The Decision to Withdraw Life-Sustaining Interventions

For some infants with severe neurologic conditions, families may face decisions regarding the provision, withholding, or withdrawal of life-sustaining treatments. These decisions are challenging for families and clinicians and may differ in important ways from similar decisions made for older children or adults.[37] For example, parents and clinicians are more likely to transition to care focused on comfort for infants at risk of life-long disability than they are for older children with a preexisting disability.[38] Typically, decisions regarding life-sustaining treatment are made by considering an infant's long-term prognosis and anticipated quality of life.[38–40] The majority of deaths in the neonatal intensive care unit, including among infants with severe neurologic injury,[41,42] occur after withdrawal of life-sustaining interventions in otherwise physiologically stable infants,[2,43] with many of these infants dying in their parents' arms following extubation.[38]

When a decision is made to withdraw life-sustaining interventions, clinicians can support the family in many important ways. Clinicians may openly discuss uncertainty around the timing of an infant's death after withdrawal of life-sustaining interventions with families. Clinicians can inquire about death-related rituals that are important to families culturally, spiritually, or in their personal belief systems, while realizing that families may not have firm ideas about what they want or what to ask for within these difficult situations.[5] Clinicians can also support families in memory-making options, such as heartbeat recordings, footprints, and photographs. Finally, it is often helpful and comforting for families if clinicians are available to offer ongoing support at the time of death. Along with the death of their child, families also experience grief related to loss of the parental role, the neonatal intensive care unit support network they have developed, and the future they had imagined for their family.[44] The interdisciplinary nature of palliative care teams, which typically include clinicians, chaplains, and social workers, can support both the family and clinical team around death and dying.

Pain and Symptom Management

Neuropalliative care teams play a key role in the management of pain and other symptoms in order to promote infant comfort and reduce parental distress.[17] Previous work has shown that pain has a negative impact on motor, cognitive, and neurodevelopmental outcomes in all infants[45,46] and on growth in preterm infants.[47] Neuropalliative care clinicians should pursue the reduction of infant pain through a wide range of interventions, from minimizing painful procedures to nonpharmacologic and pharmacologic treatments. An interdisciplinary approach, with input from neonatology, neurology, and palliative care teams, is helpful in balancing symptom management and medication side effects.

In the Neonatal Intensive Care Unit

Control of infant pain and irritability is a top priority for neuropalliative care teams. Infants with neurologic conditions are at risk for underrecognition of pain and irritability[2] due in part to scales that assess infant pain relying on changes in behavior that may not be visible in infants with significant impairment.[48–51] Existing data suggest that this problem may be compounded by a belief among clinicians that infants with neurologic conditions experience less pain than infants without neurologic conditions.[52] Infant pain can be addressed with several pharmacologic and nonpharmacologic strategies (Table 2). When possible, nonpharmacologic measures such as caregiver presence, nonnutritive sucking, swaddling, facilitated-tucking, rocking, and holding can be prioritized.[53,54] Unexplained irritability is another common and difficult-to-manage finding in infants with neurologic conditions. In addition to nonpharmacologic strategies, gabapentin may be useful in these cases to decrease reliance on opioids and benzodiazepines and improve feeding tolerance.[55]

Infants with neurologic disorders may have symptom management needs related to secretions, seizures, medication withdrawal, sleep disruption, and shivering in the setting of therapeutic hypothermia. Management of these signs may be complicated by medication interactions, side effects, development of tolerance, and altered pharmacokinetics in the setting of therapeutic hypothermia or extracorporeal membrane oxygenation. Common management strategies for these symptoms are shown in Table 2. When secretions are not adequately managed by anticholinergic medications, botulinum toxin injection into the salivary gland,[56] salivary duct ligation, or excision of the salivary gland are second-line options.

Approaching Discharge

As discharge nears, clinicians should focus on preparing parents and families to oversee their infant’s pharmacologic treatments. This includes education on dosing and administration, monitoring for common side effects as well as signs of medication toxicity. As measurement of drug levels will be less frequent in the outpatient setting, it is important that dosing regimens are safe and effective, especially in cases of polypharmacy. An infant’s dosing may change rapidly throughout the first year of life owing to weight gain and evolving symptoms, and the outpatient clinician who takes over medication management needs to be prepared to update regimens accordingly.

At the End of Life

When infant death is imminent, either due to the expected evolution of an extremely severe neurologic disorder or a decision to withhold or withdraw life-sustaining interventions, treatment should minimize suffering and maximize comfort while spending time with the family. In such cases, providing nonnutritive feedings or noninvasive oxygen support can allow for memory making and bonding. Opioids and benzodiazepines should be readily available in these situations to minimize infant pain and distress. It is important that neuropalliative care clinicians counsel families about what end-of-life may look like in their child, including the possibility of seizures accompanied by myoclonus, gasping, or apnea. Clinicians can reassure families that individualized care will be provided, considering that multiple nonpharmacologic and pharmacologic interventions are available to address end-of-life needs.

Conclusion

Neonatal neuropalliative care is an emerging field that provides tailored support to infants, families, and clinicians impacted by serious fetal and neonatal neurologic conditions. Four core domains of neuropalliative care are family-centered communication, prognostication, decision making, and pain and symptom management. Frequent and consistent family-centered communication is important, with discussions around prognostication focusing on acknowledging and reducing uncertainty, which is a reality of care and cause of distress for many families. Clinicians should engage in shared decision-making with families, working to elicit and clarify parent values while also recognizing that some decisions are made and remade over a child's lifetime. Finally, clinicians need to be familiar with unique symptom control strategies used to manage pain, irritability, secretions, seizures, withdrawal, and sleep disruption in infants with neurologic conditions. With ongoing technological advancements in life-sustaining interventions for critically ill infants, the need for neonatal neuropalliative care will continue to expand. A neuropalliative care approach can help clinicians provide longitudinal, tailored support for infants with neurologic conditions and their families.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: MEL receives salary support from the National Institute of Neurological Disorders and Stroke. Dr CH receives support for research from the National Institute of Child Health and Human Development (NIH-HHSN2752010000031).

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Table 1.

Key Considerations Across the Care Trajectory

Time period	Common diagnoses[a]	Considerations
Antenatal	Hydranencephaly Holoprosencephaly Congenital hydrocephalus Myelomeningocele Encephalocele	Prognostication relies on fetal imaging, genetic testing, and placental factors Decision making may require a balance of fetal and maternal risks
Postnatal	Intraventricular hemorrhage Post-hemorrhagic hydrocephalus Hypoxic ischemic encephalopathy Neuromuscular conditions Perinatal arterial ischemic stroke Neonatal epileptic encephalopathy	Prognostication relies on neuroimaging, electroencephalography, genetic testing, and infant examination Decisions are often remade and revisited over time; clinicians should revisit prognosis and parent values longitudinally Infants are at increased risk for underrecognition of pain and irritability

[a] Many conditions that present antenatally can also present in the postnatal period. Similarly, some common neurologic conditions of the newborn can present antenatally.

Table 2.

Pharmacologic Pain and Symptom Management[a]

Pain	Morphine Starting dose: 0.02–0.1 mg/kg IV or 0.2–0.4 mg/kg PO/SL q2-4h PRN Infusion: 0.02–0.1 mg/kg/h IV Fentanyl Starting dose: 1–3 µg/kg IV/intranasal q1-2h PRN Infusion: 1–3 µg/kg/h IV Methadone Starting dose: 0.05–0.2 mg/kg IV/PO q4-24h Oxycodone Starting dose: 0.05–0.1 mg/kg PO q4-6h Acetaminophen 10–15 mg/kg PO/IV or 20 mg/kg PR q6h Oral sucrose 24% 0.1–2 mL PO PRN
Pain and sedation	Clonidine Starting dose: 1–3 µg/kg PO q6-8h Clonidine patch 1/4–1/2 of a 0.1 mg / 24 h patch transdermally (do not exceed 12 µg/kg/d) Dexmedetomidine Starting dose: 0.5–1 µg/kg IV or 2–4 µg/kg PO/SL/buccal/intranasal q1-4h PRN Infusion: 0.2–1 µg/kg/h IV Gabapentin 5–10 mg/kg PO q8-12h Recommended for use in older infants, starting with the lowest dose; avoid in premature infants
Sedation	Midazolam Starting dose: 0.05–0.1 mg/kg IV or 0.2 mg/kg PO/SL/intranasal q1h PRN Infusion: 0.01–0.12 mg/kg/h IV Lorazepam Starting dose: 0.05–0.1 mg/kg IV/PO/SL q2-4h Diazepam Starting dose: 0.05–0.25 mg/kg PO/PR q4-12h
Secretion management	Glycopyrrolate 2–10 µg/kg IV or 20–100 µg/kg PO q6h Atropine 1 drop of 1% ophthalmic solution SL q4-6h PRN
Hypertonia	Baclofen Starting dose: 0.1 mg/kg PO q8-12h, can increase to maximum of 0.5 mg/kg/dose
Sleep disturbance	Melatonin 0.5–1 mg PO daily

Abbreviations: IV, Intravenous; PO, per os, by mouth; PR, per rectum; PRN, pro re nata, as needed; SL, sublingual.

[a] Pharmacokinetics, safety, and efficacy for many of these agents have not been well established in infants.