Pain management in hospitalized infants needs to balance 2 key considerations.1 First, infants with serious medical conditions often undergo painful interventions in the hospital (eg, surgical procedures, line placements, intubations, mechanical ventilation), and clinicians must carefully manage infants’ pain and sedation to prevent distress and adverse long-term developmental consequences, including altered pain responses. Second, adequate pain control and sedation in infants who are critically ill often requires opioids, but high doses and durations of opioids in infants are associated with adverse health and neurocognitive outcomes. These 2 considerations are often in tension and likely contribute to differing clinical approaches across hospitals. How institutions vary in their use of opioids in infants is a critical first step in establishing clinical standards and supporting quality improvement. This study by Keane and colleagues² reports the findings of a large cohort study of medically complex infants aged younger than 1 year at 47 children’s hospitals across the US between 2016 and 2022 and highlights significant variation in opioid use among institutions.

Keane et al² identified a sample of infants who were medically complex based on diagnoses of or procedures for congenital heart disease, necrotizing enterocolitis, extremely or very low birth weight, hypoxemic ischemic encephalopathy, extracorporeal membrane oxygenation, and other abdominal surgical procedures (infants with cancer and those exposed to opioids or other substances in utero were excluded). Keane et al² found that more than 75% of these infants received opioids during their hospitalization, particularly fentanyl or morphine, with a median (IQR) of 5 (2-12) days of cumulative use. Clinical factors associated with more cumulative days of opioid use included mechanical ventilation, intensive care unit (ICU) or neonatal ICU stay, and medical complexity.

Even after accounting for these clinical factors, Keane et al² found significant variation across children’s hospitals. For example, in the Northeast region alone, in 2 hospitals, fewer than one-half of infants received an opioid during their hospitalization, but in 3 other hospitals, more than 80% of infants received an opioid. Variability in opioid use was less pronounced in other US census regions, but nonetheless present across the country. Similarly, methadone use varied substantially across hospitals, as did the cumulative number of days of total opioid and methadone use. Many infants who receive high doses of opioids for prolonged periods of time (eg, after surgery for necrotizing enterocolitis³) develop physiologic opioid dependence, and the methadone use that Keane et al² observed is in part attributable to its use in opioid weaning tapers to minimize withdrawal signs and symptoms. Although most of the variability (≥80%) in opioid and methadone use was explained by patient-level clinical factors, 16% of the variability in opioid use and 20% of the variability in methadone use was explained by differences at the hospital level.

Keane et al² clearly show that individual patient needs (based largely on an infant’s medical complexity) are the most significant factor associated with opioid use. However, the hospital-level variability they observed suggests that opioid use in hospitalized infants, particularly in ICU settings, where opioid use is greatest, may benefit from standardized protocols across institutions. Hospital-level variability in opioid use likely stems from hospitals having differences in clinical approaches to infant pain, which often are local, cultural, and deeply ingrained; pharmacy formulary and available medications and doses; multidisciplinary management of infant pain, including use of nonpharmacologic approaches (eg, parental comfort, sucrose) for minor procedures (eg, heel-sticks and retinopathy of prematurity screening⁴), which may reduce the need for opioids; and differences
among who conducts pain assessments (eg, parents, nurses, or physicians), among other factors.\textsuperscript{1} Critically, although individual clinicians' practices were not examined in the study by Keane et al,\textsuperscript{2} these deserve further scrutiny. For example, longer durations of cumulative opioid exposure might have been driven by the practices of a small number of clinicians whose prescribing practices differed greatly from the rest of their colleagues.

Each of these potential contributors highlights why hospitals might consider standardizing their approaches to assessing and managing infant pain and sedation and potentially move toward more judicious use of opioids. Care for a related condition, neonatal opioid withdrawal syndrome from in utero opioid exposure,\textsuperscript{5} has similarly shown substantial variability across institutions, with large differences nationwide in the percentage of infants receiving opioid agonist treatment and duration of treatment.\textsuperscript{6} This variability spurred national recommendations for hospitals to standardize their care, including enacting institutional policies, developing novel standardized clinical assessment tools, maximizing nonpharmacologic approaches and nonopioid medications, involving parents in care and comfort, and having clear clinical targets to guide the discontinuation of opioids, when used.\textsuperscript{5} Such recommendations in turn serve as the basis for statewide perinatal quality collaboratives, which have played an important role in the dissemination and implementation of new approaches across birthing hospitals. A similar approach to minimizing variability in opioid use for pain and sedation in hospitalized infants should be a national goal. Throughout, hospitals should strive for harmonization in their use of assessment tools; there are more than 65 published scales for assessing pediatric pain in preverbal children.\textsuperscript{7} Additionally, hospitals should ensure that they use different assessment tools in preterm and term infants.

Further research would enhance the development of standardized protocols and quality improvement. Specifically, high-quality randomized clinical trials are needed across the range of medical conditions and surgical procedures that Keane et al\textsuperscript{2} studied. Throughout, patient-centered outcomes (eg, pain reduction, infant comfort, parental assessment) should be studied alongside opioid stewardship outcomes (eg, days of opioid exposure, cumulative opioid doses). Observational studies will also be needed to further document variability in opioid use nationwide. Keane et al\textsuperscript{2} studied variability among children's hospitals, and further research should also examine nonpediatric hospitals, particularly birthing hospitals providing neonatal ICU care. To the extent possible, such studies should additionally measure opioid doses and intervals, which were not available in the data studied by Keane et al.\textsuperscript{2} Research should also measure clinician-level variability, which is likely to be a key target of quality-improvement initiatives. Furthermore, studies should carefully monitor health equity. Racial and ethnic differences in pediatric pain treatment are well documented, with Black and Hispanic children often less likely to receive adequate and timely care than White children following common pediatric diagnoses and procedures.\textsuperscript{3,4,9,10}

As institutions move toward standardized approaches to infant pain, they should maintain flexibility for clinicians to prescribe opioids when they deem it necessary, since infants' pain management needs can differ significantly based on their medical complexity, as suggested by the findings of Keane et al.\textsuperscript{2} Institutions and clinicians should also recognize that less opioid use is not better per se. Rather, judicious use of opioids means carefully addressing infants' distress while also avoiding unnecessary opioid use. Since undertreated pain and excessive opioid use are both associated with adverse health and neurocognitive outcomes, striking a balance is critical.
Author Affiliations: Division of Adolescent and Young Adult Medicine, MassGeneral for Children, Boston, Massachusetts (Hadland); Harvard Medical School, Boston, Massachusetts (Hadland, Schiff); Divisions of General Academic Pediatrics and Newborn Medicine, MassGeneral for Children, Boston, Massachusetts (Schiff).

Conflict of Interest Disclosures: Dr Hadland reported receiving grants from the National Institute on Drug Abuse and personal fees from the American Academy of Pediatrics outside the submitted work. No other disclosures were reported.

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