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Early repetitive pain in preterm infants in relation to the developing brain

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SUMMARY

Infants born preterm (<37 weeks of gestation) are particularly vulnerable to procedural stress and pain exposure during neonatal intensive care, at a time of rapid and complex brain development. Concerns regarding effects of neonatal pain on brain development have long been expressed. However, empirical evidence of adverse associations is relatively recent. Thus, many questions remain to be answered. This review discusses the short- and long-term effects of pain-related stress and associated treatments on brain maturation and neurodevelopmental outcomes in children born preterm. The current state of the evidence is presented and future research directions are proposed.

Rates of preterm birth (<37 weeks gestational age [GA]) have increased worldwide, occurring in approximately 11% of live births (ranging from 5% in Europe, 8% in North America, to 18% in some African countries) and is the leading cause of neurodevelopmental disability in developed countries [1]. Of those births, over 15% are born very preterm (≤32 weeks GA), representing approximately 2% of all live births in North America [2]. Moreover, rates of neurodevelopmental problems in children born very preterm do not appear to have improved, affecting about 50% of survivors [3,4]. Infants born very preterm spend weeks to months in the neonatal intensive care unit (NICU) during a delicate and critical phase of very rapid brain development and programming of stress systems [5,6]. In the NICU, these infants require numerous invasive medical interventions to diagnose and treat life-threatening conditions. This environment contrasts greatly from the calm and protective maternal womb, thus exposing these fragile neonates to repeated highly stressful and potentially painful experiences. Aiming to reduce the number of stressful procedures and handling remains the most effective method to decrease neonatal pain-related stress [7]. Although efforts to minimize this exposure have been advocated over the last 10–15 years, these infants are still exposed to a range of two to 14 invasive procedures per day [7–9], during a time when they are particularly vulnerable to repeated procedural pain [5,10,11]. Concerns regarding long-term consequences of stress and pain in preterm neonates have long been expressed by Anand [12] and Grunau *et al.* [13]; however empirical evidence of adverse associations is relatively recent [14,15]. Here we present a review of effects of pain

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exposure on the developing CNS, followed by basic and clinical evidence that repetitive neonatal pain exposure in very preterm infants is associated with altered brain development, as well as considerations of pain management in the NICU.

Pain & the immature nervous system

The late second and the third trimesters of gestation are critical periods in the development of the infant brain microstructure, when neuronal systems are more sensitive to external stimulation that is developmentally unexpected. Infants born very preterm are exposed to prolonged neonatal intensive care during a period of rapid neuronal proliferation and cell differentiation such as oligodendroglial maturation, differentiation of subplate neurons, formation of synapses, cerebellar neuronal proliferation and migration, and major axonal development in the cerebrum [11]. Thus, during this highly complex and intertwined series of processes, exogenous and/or endogenous insults to white matter tracts (i.e., decreased myelination) and subcortical structures will lead to detrimental effects on neuronal migration and cortical development. Repeated exposure to invasive procedures places very preterm infants at particular risk, due to the possible interference with the extensive developmental mechanisms and functional changes taking place in the CNS during the period in the NICU [16,17].

Initially, skin is hyperinnervated and as postnatal age increases, the exuberant epidermal innervation gradually retracts [18,19]. Many nociceptive physiological maturational processes (e.g., receptive field properties, action potential shape, receptor transduction) [19], take place over a time when preterm infants are often over-stimulated and stressed. The development of neural circuitry is influenced by sensory experience during specific critical periods early in life and this phenomenon is especially evident in the developing cortex. During the early postnatal period in rodents (comparable to preterm human neonates), sensory circuitry maturation and organization in the CNS is dependent on stimulation, for example if the somatosensory system is chemically blocked (by blocking *N*-methyl-D-aspartate receptors, which are involved in the pain transmission pathway), normal activity-dependent sensory maturation is disrupted [20]. However, over-stimulation can have damaging effects as well. Furthermore, the immaturity of descending inhibitory mechanisms (i.e., endogenous analgesic system that dampens the nociceptive inputs) makes the developing infant more sensitive to persistent sensory stimuli, which impacts central pain processing [20]. Thus, the effects of both noxious and innocuous stimuli will generally be enhanced and last longer in the premature neonate due to anatomical and functional differences in the spinal sensory connections.

Consequences of repeated neonatal exposure to stress and pain on the developing nervous system and nociceptive processing have been examined in rodent models [21]. Repetitive needle pricks during the first week of life in rat pups (roughly 24 weeks to term-equivalent age in humans) had acute and long-term effects on nociceptive circuits, showing increased afferent fibers in the spinal cord but no changes in the peripheral nociceptive innervation [22], and altered behavior, in adulthood [23]. Neonatal persistent inflammatory pain led to similar results [24]. Specifically, newborn rats injected with an inflammatory agent causing long lasting pain, exhibited as adults, higher evoked firing rates in response to innocuous touch and noxious pinch in comparison to control rats, as well as having lower withdrawal latency thresholds to noxious thermal stimulus. By contrast, mouse pups exposed to laparotomy at birth showed decreased nociceptive sensitivity (i.e., elevated latency to react to hot-plate and tail-flick testing) in adulthood compared with controls [25].

In human clinical studies, neonatal exposure to noxious insults and surgical procedures during NICU stay is associated with altered basal nociceptive processing in infancy and

childhood [26–29]. Specifically, repetitive pain-related stress in preterm infant has been shown to have long-term consequences on children's somatosensory processing (i.e., quantitative sensory testing) [27–29], sensitivity to pain [30,31] and response to pain [32–34]. For example, children who had NICU experience (regardless of developmental age at which it took place) were shown to have greater perceptual sensitization to tonic heat compared with controls, which is indicative of altered central sensitization [29]. However, this study included both preterm and full-term infants exposed to pain in the NICU, rendering the results somewhat difficult to interpret.

Lower thresholds to mechanical touch on injured heel from repeated heel lances for blood sampling during NICU stay were described in preterm infants during the first year of life compared with term-born controls [27]. Additionally, hypersensitivity in the first days to weeks of life in injured heel (ipsilateral) compared with contralateral heel was also demonstrated. During the first year of life, longer length of stay in the NICU, possibly indicating a greater pain-related stress exposure, was associated with higher pain expression in response to immunization in former very preterm infants [34]. Grunau and colleagues reported parent ratings of lower sensitivity to common hurts at 18 months in very preterm toddlers born at extremely low birthweight (<1001 g) compared with preterm toddlers born at heavier weight (>1500 g) and full birthweight (>2500 g) [33].

At later ages, decreased sensitivity to thermal (mediated by unmyelinated C-fibers and A-δ fibers) but not mechanical (A-β sensory function) stimuli was demonstrated in 11 year-old children born extremely preterm (less than 26 weeks GA) in comparison to children born at full-term [28]. Unexpectedly, this observed hyposensitivity was more marked in those who had undergone surgery as a neonate.

In parallel to the experience-driven development of the somatosensory system, early life exposure to stress can significantly affect the functional maturation of limbic circuits [35], which will also impact emotional pain perception and experience. Increased somatization (pain of unknown origin) at age 4–5 years in preterm children born at extremely low birthweight (≤1000 g) [36] compared with full-term born children, has been reported. Greater catastrophizing to painful events has been demonstrated in children and adolescents born very preterm [37]. However, there is limited knowledge of attention, memory and cognitive factors in relation to the changing perception of pain from infancy through childhood in very preterm children [21].

Neonatal pain in relation to brain development

In the preterm population, altered brain development is evident in early infancy [38–40] and at school-age [41–45]. Compared with term-born peers, preterm children show reduction in gray and white matter volumes in infancy, childhood and adolescence [14,42,43,46,47], as well as abnormalities in cortical thickness [46,48–53]. For example, volumetric MRI and diffusion tension imaging (DTI) analyses have demonstrated decreased regional volumes (e.g. in cerebellum, thalamus, cerebral cortex) and possible axonal disturbances in very low-birthweight neonates from term-equivalent age to later in adulthood [11]. Sensorimotor, premotor, temporal and parieto-occipital regions are generally reported as the cortical regions showing the most significant volumetric reductions in preterm born school-age children and adolescents [41,42,43,54,55].

However, few studies have evaluated neonatal factors that may contribute to altered brain development in this population, or addressed potential underlying mechanisms. Recently Inder and colleagues [40] showed that greater exposure to stressful procedures (e.g., heel lance/venipuncture, intubation/extubation, diaper change) in the NICU was associated with reduced brain size in the frontal and parietal regions in preterm neonates assessed at term-

equivalent age. In addition, in that study, functional connectivity MRI and DTI measures showed that alteration in brain microstructure and functional connectivity within the temporal lobes were related to greater stress exposure. Similarly, Grunau and colleagues found that greater exposure to neonatal procedural pain (adjusted for multiple neonatal clinical factors) was associated with reduced maturation of white matter and subcortical gray matter in a cohort of very preterm infants scanned early in life and again at term-equivalent age [14]. Thus, these studies converge to reveal the importance of early stressful and painful procedural events on adverse brain development.

Early-life adversity in animal models, including maternal separation [56–59] and pain exposure [23,60–63], induces long-term neurobiological and behavioral changes [64,65]. To our knowledge, only a few studies in the neonatal rodent model have specifically examined pain and altered brain development. Early inflammatory pain in neonatal rodent pups induced increased cortical and subcortical neuronal activation [66], increased hippocampal gene expression [67] and widespread cell death [66,68], thus modifying both the structure and function of the developing brain [68]. Persistent inflammatory pain (formalin injections) or repetitive pain (saline injections) may induce major neuronal apoptosis and altered expression of developmentally important proteins in the rat pup brain during the first week of life [68]. The most degenerated cells were found in the lamina II of both frontal and parietal cortex. Importantly, there were differences in long-term effects on the adult brain depending on the timing and type of neonatal pain [68]. Given that the majority of the neonatal painful procedures occur within the first weeks of the NICU stay, especially in those that are born very preterm and who undergo the most procedures [14], addressing the management of procedural pain-related stress to protect the developing brain in preterm infants is pressing.

Understanding how responses to nociceptive stimuli evolve, and how brain activity related to pain changes with development, is essential in order to accurately delineate pain processing in preterm infants [69]. Early in development, innocuous and noxious stimulations evoke neuronal bursts on electrophysiological recordings. As touch and pain discrimination develops around 35–37 weeks gestation, a transition from generic evenly spread neuronal bursts to stimulus-specific activity takes place [69]. Consequently, discrimination between innocuous and noxious stimuli is challenging in very preterm infants due to their immature somatosensory system. Thus, the highly sensory stimulating environment of the NICU may have additive or cumulative effects on the developing CNS and stress system of preterm infants. Furthermore, higher neuronal activity in response to heel lance was shown in preterm compared with age-matched term-born neonates [70]. It is also possible that this increased neuronal excitation could be detrimental to preterm neonates' immature and rapidly developing neuronal network by altering apoptosis (programmed cell death) and neural survival [71].

The authors' understanding of the extent to which neonatal pain and stress exposure may impact neurodevelopment in immature neonates is still emerging, and basic animal research is crucial to determine mechanisms. Nonetheless, a series of studies by Grunau and colleagues from two prospective longitudinal cohorts of infants born very preterm are providing some converging indications. Greater exposure to neonatal pain-related stress, after controlling for multiple confounding neonatal clinical factors, was shown to be associated with altered brain microstructural development (subcortical gray matter and white matter) from early in life to term-equivalent age [14]. Additionally, in this same cohort of very preterm infants, illness severity in the first 24 h of life together with pain exposure (quantified as the number of skin breaking procedures from birth to term-equivalent age), was found to contribute to slower microstructural development of the corticospinal tract up

to term-equivalent age [72]. Together, these findings suggest the importance of protecting the developing brain during the first days of life.

In an older cohort from the same site, detrimental effects of neonatal repeated pain-related stress appear to not only have short-term effects on white and subcortical gray matter development but also have long-term consequences in children born very preterm [15]. Recently it was demonstrated that greater neonatal procedural pain, after controlling for neonatal clinical factors related to preterm birth, was associated with reduced cortical thickness in multiple brain regions at 7 years in children born very preterm [15]. More precisely, cortical regions found to be the most sensitive to pain exposure were the pre/post central and frontal areas. Importantly, among the neonatal clinical factors included in the statistical model (e.g., gestational age at birth, illness severity on day 1, days on mechanical ventilation, cumulative dosage of morphine), pain exposure was the most robust predictor of cortical thickness. Furthermore, using magneto-encephalography, in the same cohort Doesburg *et al.* found that altered functional brain activity, characterized by higher ratio of γ-to-α oscillations, was related to greater exposure to cumulative neonatal pain adjusted for medical confounders in extremely preterm infants (born ≤28 weeks GA) at school-age, which was not seen in very preterm (28–32 weeks GA) and full-term children [73]. These findings provide foundational work for future research investigating neonatal pain-related changes in cerebral activity within specific brain systems and neurodevelopmental outcome in other functional domains.

Neonatal pain in relation to cognitive, motor & behavioral outcomes in infants & children born preterm

In animal models of neonatal pain, specific patterns of long-term behavioral effects from exposure to repetitive acute pain or prolonged inflammatory pain in the first week of life of rat pups have been demonstrated, such as decreased locomotor activity [60] and increased defensive withdrawal behavior [23] in adult rats exposed to neonatal pain. During the first week of life severe inflammatory pain from formalin injections, and pain caused by repeated saline injections, may induce neuronal apoptosis and altered expression of developmentally important proteins in the rat pup brain [68], however, the findings were complex.

Converging findings in preterm born children exposed to pain during their stay in the NICU are emerging. Exposure to repeated pain in very preterm infants in the NICU is associated with altered cognitive and motor development [5]. Recently, neonatal pain exposure (quantified as the number of neonatal skin-breaking procedures adjusted for clinical confounders) was associated with deleterious effects on postnatal body and head growth at 32 weeks postconceptional age [74]. At school age, greater neonatal pain exposure in extremely preterm born children was found to be associated with altered brain activity, which in turn, impacted their visual perceptual abilities [73].

Internalizing behaviors (i.e., depressive and/or anxious), prevalent in children born very preterm compared with full-term, are evident in the second year [75,76] and persist to school age, late adolescence and young adulthood [77–81]. Moreover, greater neonatal pain exposure (adjusted for neonatal clinical factors) was associated with greater internalizing behaviors at 18 months corrected age (CA; i.e., age of the child from the expected date of delivery) [76], persisting to age 7 years [82]. In very preterm infants, greater cumulative exposure to neonatal pain-related stress has been associated with altered developmental trajectory of stress hormone (cortisol) expression (i.e., programming of the hypothalamic–pituitary–adrenal axis) long after NICU discharge [83,84]. Together, animal and human clinical studies are providing evidence for short- and long-term detrimental effects of neonatal pain-related stress exposure on neurodevelopmental outcomes in preterm infants.

However, studies linking pain-related alterations to brain development and thereby with cognitive, motor and behavioral outcomes in very preterm children are only recently emerging. Based on evidence so far, this line of research is expected to greatly enhance our understanding of the impact on the immature CNS of early repeated pain and stress exposure.

As mentioned previously, during their NICU care, preterm neonates are exposed to multiple factors that may alter brain development, and teasing out specific pain-related effects is challenging. Pre- and post-natal clinical factors and treatments might interact or may lead to similar end points, which makes them difficult to isolate [10].

Pain treatment strategies, brain development & neurodevelopmental consequences

Human trials in preterm infant pain and opioid therapies are extremely difficult to conduct due to numerous confounding medical factors and crossover of study arms (i.e., exposure of control group to study drug), thus, we rely on preclinical studies to provide complementary data to inform and improve clinical care. However, whereas animal studies have significantly improved our understanding of the possible short- and long-term effects of neonatal pain and analgesic treatments, models that more directly reflect the NICU experience are needed. Importantly, the physiological immaturity of preterm neonates and their developing neuronal circuitry renders them particularly vulnerable to stress. Major gaps in knowledge remain. Importantly, opioids appear to have differing effects in the presence or absence of pain. In rat models, pre-emptive morphine only protected neonatal pups against long-term brain and/or behavioral changes when pain was present at the time of opiate exposure [60,68,85].

Large-scale randomized controlled trials in The Netherlands [86] and primarily in the USA (NEOPAIN [87], and cohort studies [e.g., the EPIPAGE cohort in France [88]]) have examined long-term effects of routine use of morphine infusions in mechanically ventilated preterm infants [89–92]. Based on findings from the randomized controlled clinical trials [87,86] concerns of short-term effects of pre-emptive morphine infusion on neurological outcomes of ventilated preterm infants, judicious use of intravenous morphine analgesia is now recommended. Routine treatment of pain with morphine is no longer advocated in ventilated preterm infants in the NICU [93], since in the short-term, continuous morphine infusions lead to longer duration of mechanical ventilation and longer time to reach full enteral feeding [87], and concerns remain about long-term effects of analgesia and sedation on the developing brain [86,87,90,91,93,94]. Nevertheless, morphine did not appear to significantly increase the short-term risk of major adverse neurological outcomes such as severe intraventricular hemorrhage (IVH grade 3 and 4) or periventricular leukomalacia, and in the trial conducted in The Netherlands [86], the incidence of all grades of IVH was significantly lower in the morphine group compared with controls. However, morphine lacked beneficial effects for pain treatment, as pain scores were not clinically lower in infants that received morphine infusions [86,87]. Importantly, in both trials, open-label morphine was administered in 34% [86] and 50% [87] of the preterm infants enrolled, and when controlled for in statistical analyses, rates of death or incidence of severe IVH or periventricular leukomalaciawere significantly higher in the morphine group [87]. Higher doses of morphine were administered to neonates in the NEOPAIN trail [87] (10–30 μg/kg/h) compared with the Dutch trial [86] (10 μg/kg/h), which may explain the differing results.

Follow-up studies of these trials on long-term cognitive, motor and behavioral outcomes in relation to morphine exposure have also reported mixed findings [89–92]. At 5 years, no significant differences in intelligence, behavior or visual–motor function were found

between preterm born children in the morphine group and those in the placebo group (adjusted for open-label morphine administration) [90]. Neonatal morphine exposure had no effect on internalizing behaviors at 5 years [90,92] or at 8–9 years [89]. The most recent findings suggest a possible neuroprotective effect of pre-emptive morphine infusion on some aspects of parent report of executive functions at 8–9 years in children born preterm [89]. However, in that study, morphine was not found to be beneficial on teacher reports or on individual testing of child executive functions, thus the results remain tentative. By contrast, preliminary long-term follow-up results from the NEOPAIN trial found that the preterm neonates exposed to pre-emptive morphine infusion had smaller head circumference and showed longer choice response latency in a short-term memory task at 5 years of age [92]. All these findings should be interpreted taking into account that the extent of neonatal pain exposure was not considered in those studies, and the differing morphine dosage in the two trials. Lastly, an earlier randomized controlled trial, albeit a small sample, reported that exposure to morphine infusion for less than 7 days in the neonatal period in children born preterm did not appear to have damaging effects on neurodevelopmental and behavioral outcomes at 5 years [95].

From a large population-based study in France (EPIPAGE [88]), Rozé and colleagues found that very preterm infants who received prolonged sedation and/or analgesia in the NICU were at no greater risk of motor and cognitive disabilities at age 5 years, after adjusting for multiple neonatal factors [91]. In a single-site cohort study of very preterm children in Canada, Grunau and colleagues reported that greater cumulative exposure to neonatal intravenous morphine (controlling for the number of invasive procedures) was associated with poorer motor development at 8 months, but not at 18 months CA [5]. Correspondingly, from early in life to term-equivalent age, greater neonatal morphine exposure was associated with adverse effects on growth of the cerebellum, a brain region known to play an important role in motor control [96]. Conversely, in an independent cohort from the same site, cumulative morphine exposure during NICU care was not associated with either a positive or deleterious effect on postnatal body and head growth at 32 weeks postconceptional age [74]. Finally, at school-age, higher exposure to neonatal morphine appeared to be adversely associated with internalizing behaviors in very preterm children who underwent mechanical ventilation during NICU care [82]; however, no such association was found in preterm children at age 5 and age 8–9 years from the trial in The Netherlands [89,90].

By contrast, morphine may prevent altered nociceptive responses. Earlier preliminary findings from Grunau and colleagues showed that greater exposure to morphine in the NICU was associated with a more ‘normalized’ pain response in extremely low birth weight infants at 8 months chronological CA [13]. These findings are supported by animal work [60,85]. In summary, exposure to higher morphine dosing in very premature neonates may have short-term adverse consequences on motor and cerebellar development. Effects on children’s behaviors at school age are inconclusive at this point. However, cumulative neonatal morphine exposure may have a possible protective effect on nociceptive systems in preterm infants.

Fentanyl is another opiate commonly used in the NICU but long-term effects remain uncertain [97]. Thus, its routine use for management of ventilated preterm neonates has also not been recommended [93]. The impact of other commonly used analgesia and sedation strategies, used alone or in combination, such as intravenous acetaminophen, NSAIDs, ketamine, clonidine, propofol and tramadol, also need to be considered in future studies [97]. Furthermore, with advancements in pain treatments used in neonatal and pediatric intensive care, such as the growing interest in dexmedetomidine [98] and ketobemidone [99], it will be important to further examine the impact of these newly used strategies on brain development of this vulnerable population. Given that analgesic receptors in the brain

of young infants are still immature and developing, integrating the study of developmental neurobiology of pain processing has been proposed as an important consideration for future pharmacology trials [19].

Nonpharmacological treatments of pain

Several approaches for pain management of the preterm infant have been studied and are used in NICUs across the world, including sucrose, facilitated tucking, skin to skin/kangaroo care, nonnutritive sucking, breastfeeding, swaddling (for reviews of nonpharmacologic pain treatments see [100–102]). Among those, sweetening agents (primarily sucrose) have been recommended extensively [103] and is currently the standard practice in many NICUs worldwide. However, little is known about the mechanism of this therapy in humans, and the long-term developmental effects of repeated exposure, especially in the most immature preterm infants [104–106]. To date, only one study has evaluated neurodevelopmental effects of repeated administration of sucrose in very preterm infants and showed that greater exposure (>10 doses in 24 h) was associated with poorer motor and attention at 36 and 40 weeks post-conceptual age [107]. Rising evidence is pointing to the effects of sucrose/carbohydrates on regulation of the hypothalamic–pituitary–adrenal axis – the neuroendocrine system responsible for controlling responses to stress [108]. Of additional concern is the use of sucrose in combination with opioids such as morphine, given that chronic administration of sucrose in rat pups has been shown to have opiate-like effects on dopamine-receptive gene expression later in adulthood [109]. In fact, both morphine [110,111] and sucrose [109,112,113] were shown to decrease levels of dopamine receptor D2 in the rodent brain. Despite the fact that the recommended maximum daily dose is <10 doses, studies have reported the amount administered as high as 24 doses per day [114]. Future studies are needed to focus on the long-term developmental effects and neurodevelopmental outcomes of chronic exposure to sweetening agents in preterm children, with a particular attention on dose exposure.

Conclusion & future perspective

Altered brain development is evident in preterm children. During their NICU care, preterm neonates are exposed to multiple factors that may alter the developing brain, and teasing out specific pain-related effects is challenging. Prenatal and post-natal clinical factors and treatments might interact or may lead to similar end points, which makes them difficult to isolate [10]. Recently, neonatal procedural pain/stress exposure has been identified as being significantly associated with specific changes in brain development seen in this population, independent of other factors associated with prematurity. However, many questions remain to be answered. Blending basic science models and clinical research in an integrated approach will greatly improve our understanding of the complexities associated with pain-related stress in the context of preterm birth and extended NICU experience. Preclinical studies allows control of specific potential confounding factors, thus providing confirmatory evidence for findings in clinical research [21]. Thus, further research in neonatal animals that more closely model pain in the NICU environment, are necessary to determine the short- and long-term impact of pain-related stress and its related treatments on brain development and neurodevelopmental outcomes. Finally, it remains for future studies to evaluate to what extent brain alterations associated to neonatal pain exposure are related to cognitive, motor and behavioral outcomes in these infants.

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Practice Points

- Preterm infants are in the neonatal intensive care unit (NICU) during a critical period of rapid brain development.
- Infants born preterm are particularly vulnerable to stress and pain exposure.
- Understanding of how early stressful experiences impact the brain and neurodevelopment in the short- and long-term is only emerging.
- Evidence is now pointing to pain-related stress and possibly some pain treatment strategies as having short- and long-term effects on brain development and neurodevelopmental outcomes.
- Further studies are needed in animal models that more closely reflect NICU experience, and in the human clinical NICU setting.