



Day-Night Activity in Hospitalized Children after Major Surgery: An Analysis of 2271 Hospital Days

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Objectives To characterize the day-night activity patterns of children after major surgery and describe differences in children's activity patterns between the pediatric intensive care unit (PICU) and inpatient floor setting.

Study design In this prospective observational study, we characterized the daytime activity ratio estimate (DARE; ratio between mean daytime activity [08:00-20:00] and mean 24-hour activity [00:00-24:00]) for children admitted to the hospital after major surgery. The study sample included 221 infants and children ages 1 day to 17 years admitted to the PICU at a tertiary, academic children's hospital. Subjects were monitored with continuous accelerometry from postoperative day 1 until hospital discharge. The National Health and Nutrition Examination Survey accelerometry data were utilized for normative data to compare DARE in a community sample of US children to hospitalized children.

Results The mean DARE over 2271 hospital days was 57.8%, with a significant difference between the average DARE during PICU days and inpatient floor days (56% vs 61%, $P < .0001$). The average subject DARE ranged from 43% to 73%. In a covariate-adjusted mixed effects model, PICU location, lower age, orthopedic or urologic surgery, and intubation time were associated with decreased DARE. Hospitalized children had significantly lower DARE than the National Health and Nutrition Examination Survey subjects in all age groups studied, with the largest difference in the youngest PICU group analyzed (6-9 years; 59% vs 75%, $P < .0001$). A subset analysis of children older than 2 years ($n = 144$) showed that DARE was <50% on 15% of hospital days.

Conclusions Children hospitalized after major surgery experience disruptions in day-night activity patterns during their hospital stay that may reflect disturbances in circadian rhythm. (*J Pediatr* 2019;209:190-7).

Sleep plays an integral role in brain development, which is reflected by the constantly evolving sleep needs of infants and children as they grow.¹⁻³ Hospitalized children are exposed to several factors that can disrupt sleep continuity during a critical time in brain development and recovery, including pain, noise, light, and interruptions for nursing care. After major surgery, children admitted to the pediatric intensive care unit (PICU) are often exposed to sedative and analgesic medications that also have negative effects on circadian rhythms.⁴⁻⁶ Normal sleep-wake homeostasis is critical for thermoregulation, minimizing inflammation, and maintaining normal immunity.^{5,7-9} In addition, circadian rhythm impairments may increase the risk of delirium in the PICU, which is associated with increased cost, hospital length of stay, and mortality.¹⁰⁻¹⁴ Moreover, these alterations in sleep continuity that begin after surgery may persist beyond the PICU on the inpatient floor and even after discharge to home.^{15,16}

Although polysomnography is considered the gold standard for objective assessment of sleep architecture, its application is limited for continuous, longitudinal measurement in the hospital setting. Actigraphy is a noninvasive, well-tolerated, reliable, and objective method to assess 24-hour patterns of day-night activity over several days to weeks.¹⁷⁻²¹ Validated for sleep assessment in infants and children,^{22,23} the wristwatch-like device produces minute-to-minute activity counts to monitor activity patterns over the course of hospitalization.

To date, no studies have objectively described the day-night activity patterns of hospitalized children. Adult studies have shown that circadian rhythm disturbances persist during the course of short- and long-term recovery from surgery.^{24,25} Such findings may have even more extensive implications in a

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DARE	Daytime activity ratio estimate
ICU	Intensive care unit
NHANES	The National Health and Nutrition Examination Survey
PICU	Pediatric intensive care unit
PRISM	Pediatric risk of mortality score

population undergoing active neurocognitive development. Therefore, it is critical to characterize rest-activity patterns in hospitalized children to inform potential targets for intervention. The primary objective of this study was to characterize the day-night activity patterns of infants and children after major surgery and describe the differences in children's activity patterns as they transition from the PICU to an inpatient floor setting. In addition, we aimed to demonstrate the feasibility of continuous actigraphy monitoring in a heterogeneous group of pediatric patients in the hospital setting and compare their activity patterns to those of a community sample of US children using a novel analytic technique, the daytime activity ratio estimate (DARE).

Methods

The reporting of this study conforms to the STROBE statement for reporting of observational studies.²⁶ Children were eligible for inclusion if they were admitted to the Johns Hopkins PICU after major cardiac, orthopedic, or urologic surgery. We chose to include these groups of surgical patients because they comprise a large proportion of surgical PICU admits; capture a wide range of ages while minimizing the heterogeneity in comorbid conditions that could confound the DARE (ie, neurosurgery, general pediatric surgery); and are generally admitted for greater than 1 night after surgery. The Johns Hopkins PICU is a 40-bed, academic, tertiary-care PICU, which serves all medical and surgical patients who require critical care in the pediatric setting. Informed consent was obtained on the day after surgery from the child's parent or legally authorized representative, and assent was obtained from the child when age or developmentally appropriate, unless the child was mechanically ventilated and receiving sedatives. Consent was delayed until postoperative day 1 to avoid increased parental stress on the day of surgery in the setting of a high-risk procedure. Patients were excluded if they had evidence of seizure activity at the time of screening, a history of traumatic brain injury, severe obstructive sleep apnea, ischemic or hemorrhagic stroke, or neuromuscular disease. The study was approved by the Johns Hopkins Institutional Review Board.

Demographic and clinical data collected by daily chart review through the duration of actigraphy recording included age, sex, type of surgery (cardiac/orthopedic/urologic), length of PICU stay, floor and hospital length of stay, pediatric risk of mortality score (PRISM)-3, intubation status, and duration of mechanical ventilation.

DARE

Though the actigraph can estimate the duration of sleep and wakefulness using algorithms that quantify the reduced movement associated with sleep, these algorithms may overestimate the amount of time in sleep owing to a state of bed-rest or immobility in the hospital setting, particularly in the intensive care unit (ICU).²⁷⁻²⁹ In healthy children, activity is consolidated during the daytime hours, and the rest-

activity cycle can be used as an indirect measure of the sleep-wake cycle. For this reason, we introduce a simple, reliable, and normalized measure of differences between day and night activity patterns that uses an explicit, easy-to-reproduce algorithm based directly on the raw motor activity data.³⁰ The DARE is defined as the ratio between the mean daytime activity (08:00-20:00) and the mean 24-hour activity (00:00-24:00). When minute-level activity data are available, computing DARE is straightforward and reproducible across studies. Major advantages of DARE are that it is intuitive and simple, has the same interpretation across subjects and days, and is reproducible across platforms and software.^{31,32} The DARE can be compared easily across subjects regardless of age, disease process, or neuromuscular strength.

Actigraphy in Hospitalized Children

An actigraphy watch (MicroMotionlogger; Ambulatory Monitoring, Inc, Ardsley, New York) was placed on the child's wrist or ankle on postoperative day 1 in the PICU, and remained in place until the day of hospital discharge. The MicroMotionlogger has been used widely to document rest-activity patterns in infants and children.³³ Motion sensors inside the accelerometry device capture data on patient movement using the Zero Crossing Mode, which is measured as the number of accelerations per minute. The devices used in this study are capable of collecting data for up to 12 weeks. If the child was intubated at the time of actigraphy initiation, data analysis began at the time of extubation because of the confounding effects of sedation and immobilization (ie, restraints) on activity data. Act Millennium software was used for downloading the actigraph data, and initial data pre-processing was conducted using ActionW 2.7 software (Ambulatory Monitoring, Inc, Ardsley, New York).

A member of the research team monitored each subject's device daily to document that it was in place, comfortable, functioning, and not interfering with the child's medical care. A log placed at the bedside of each subject was used to record times that the actigraphy device was removed for patient care activities (eg, intravenous access, baths); travel to surgical, diagnostic, or interventional areas (eg, magnetic resonance imaging); or parent/child request. The research team reviewed this log daily during visits and queried family and nursing staff to ensure completeness.

Actigraphy in a Community Sample

Accelerometry data used to obtain estimates of normative DARE in a representative sample of children in the US were collected during the National Health and Nutrition Examination Survey 2003-2004 and 2005-2006 waves³⁴ and is available in processed format in the rnhanesdata package (Baltimore, Maryland).³⁵ This NHANES sample examined individuals 6 years of age and older. The device employed was a uniaxial accelerometer manufactured by Actigraph (Pensacola, Florida), placed at the hip. The study protocol instructed participants to remove their accelerometers during sleep. However, using established algorithms for estimating

nonwear time, it was determined that a subset of participants was noncompliant and wore the device during sleep on 1 or more days.^{36,37} In estimating normative DARE, we included days with more than 22 hours of estimated wear-time, resulting in a total of 1122 days across 565 participants in 3 age groups (6-9 years, 10-13 years, and 14-17 years). The number of participants in each age group was 161, 175, and 229, respectively. The NHANES sample included more male (324) than female (241) children, and was 15% white, 23% Mexican American, 54% black, and 8% other race. Age trends in DARE were consistent across race in this sample.

Actigraphy Data Analysis

For subjects with complete actigraphy data, activity profiles represented by 1440 minute-level (24 hours) activity counts were analyzed. A log (count+1) transformation was applied to reduce the strong skewness of the activity count distributions. Transformed activity counts were averaged within 2 specific time periods: daytime (08:00-20:00) and night-time (20:00-08:00). Day-night activity patterns were estimated by using DARE, defined as the ratio of the average daytime activity to total 24-hour activity. More precisely, $DARE = \bar{y}_d / (\bar{y}_d + \bar{y}_n)$, where \bar{y}_d and \bar{y}_n are the average log activity counts (per minute) for an individual during the daytime and night-time hours, respectively. A DARE of 100% indicates that all activity is occurring during the daytime period with consolidation of rest at night, whereas a DARE of 50% suggests that the level of activity is equally distributed between day and night periods. Assuming an average DARE of 75% in healthy children, we aimed to enroll 200 subjects to demonstrate a 15% decrease in average DARE in hospitalized children with $\alpha = 0.05$ and 90% power.

Thus, DARE was calculated for every child and every day. To account for the multilevel structure of the hospital data (multiple days measured within the same child), a mixed effects model with child-specific random intercepts was used. We examined the fixed effects for the PICU, sex, age, race, PRISM, cohort, and time intubated in minutes. Because the distribution of time intubated was highly skewed, the transformation $\log(\text{time intubated} + 1)$ was applied. All analyses were performed using the `lme()` function in the `nlme` (v 3.1-131) package in R 3.4.2.³⁸

Results

During the study period, 250 children were enrolled in the PICU, 221 of whom met the criteria for completion of the study with >24 hours of analyzable actigraphy data (n = 2271 hospital days). Eighty-four percent of eligible admissions (n = 333) were approached for informed consent during the study period and 90% of these patients were enrolled. Only 6 children dropped out of the study before hospital discharge owing to some discomfort in wearing the actigraphy watch. However, the watch was associated with no adverse events (eg, irritation, constriction). One watch was lost or misplaced before study completion.

Table I. Baseline patient characteristics by surgical cohort

Variables	Cardiac	Orthopedic	Urologic	All patients
Number (%)	143 (64)	64 (29)	14 (6)	221
Age, mean (SD), mo	61 (68)	149 (55)	58 (74)	86 (76)
Weight, mean (SD), kg	21 (20)	36 (18)	19 (18)	25 (21)
Male sex, n (%)	92 (64)	23 (36)	9 (64)	124 (56)
PRISM score, mean (SD)	8 (5)	6 (5)	3 (5)	7 (5)
PICU LOS, mean (SD), d	9 (17)	7 (9)	11 (13)	9 (15)
Intubated at admission, n (%)	70 (49)	18 (28)	0	88 (40)
Race, n (%)				
White	73 (51)	37 (58)	12 (86)	122 (55)
Black	39 (27)	9 (14)	0	48 (22)
Other	31 (22)	18 (28)	2 (14)	51 (23)

LOS, length of stay.

Demographic and clinical characteristics of the patient sample are shown in **Table I**.

When all patients (n = 221) and hospital days (n = 2271) were included, the mean daytime activity represented 57.8% (95% CI 57.4%-58.2%) of total activity while in the hospital and ranged from 4.6% to 98.6% (**Figure 1**). The mean DARE was 55.9% (95% CI 55.4-56.4) during 1346 PICU days and 60.8% (95% CI 60.1%-61.5%) during the 905 days on the inpatient floor ($P < .0001$). Children in the cardiology cohort had the highest mean DARE (58.2%; 95% CI 57.7-58.7) when compared with the orthopedic (57.5%; 95% CI 56.6-58.4) and urology (57.0%; 95% CI 56.1-57.9) cohorts. The average subject DARE ranged from 43.1% to 73.2%, and 11 subjects (5%) had <50% of their average daily activity occur during daytime hours (**Figure 2**; available at www.jpeds.com). Eighteen percent of all hospital days had a DARE less than 50%. **Figure 3** illustrates actigraphy plots for a spectrum of DAREs, with all patient days organized from lowest to highest DARE.

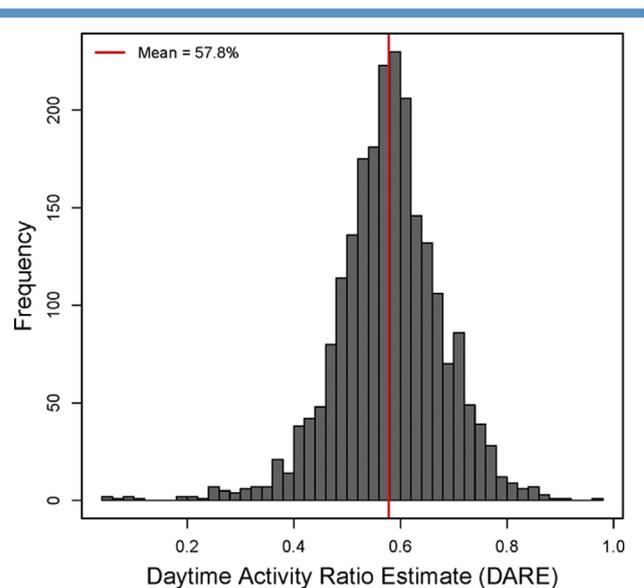


Figure 1. Histogram of DARE over all hospital days.

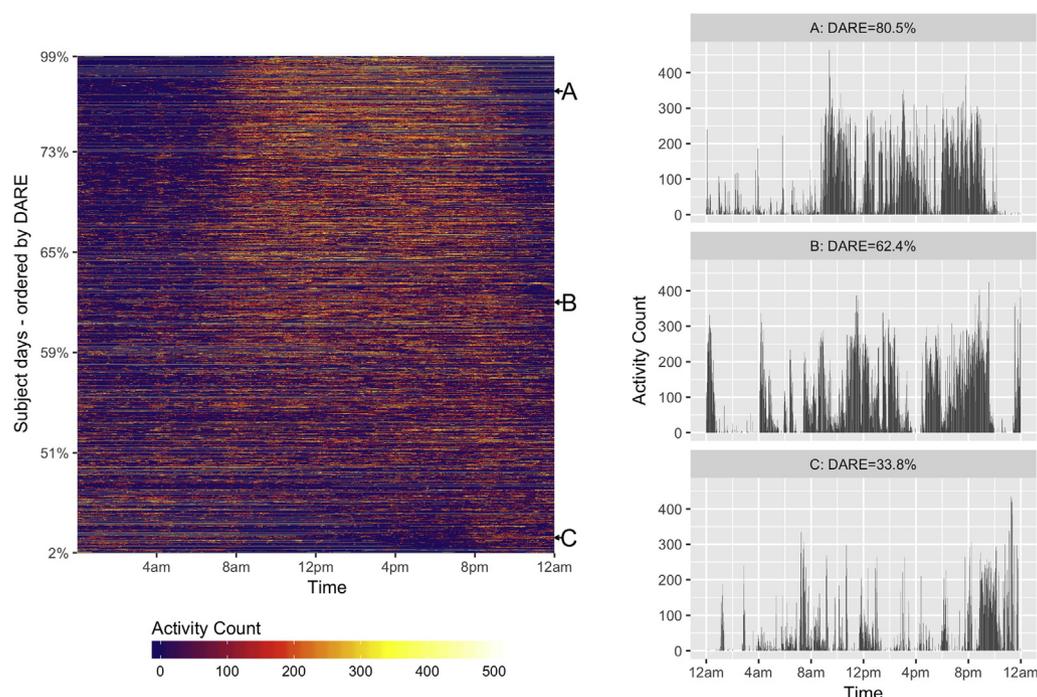


Figure 3. Left, Heat map of 24-hour activity arranged by DARE. Note the clear transition to consolidated rest-activity patterns above 60%. Right, Twenty-four-hour actigrams for DAREs at points A, B, and C in the left panel.

To determine predictors of DARE, we fit a mixed model with random intercept for each subject while controlling for age, sex, patient location, surgical cohort, PRISM score, log of time intubated, and race (Table II; available at www.jpeds.com). PICU days were associated with a significantly lower DARE (-5.3% , $P < .0001$) than were days when the subject was on the floor. After adjustment, the urology cohort exhibited the lowest DARE when compared with the reference cardiology cohort (-5% , $P = .0001$). The log intubation time was associated with lower DARE. As an example, for each 20% increase in intubation time (eg, from 10 days to 12 days), the DARE decreased on average by 0.12%. Older children had a higher DARE, with a 0.18% increase for each year of age. Severity of illness at PICU admission was not associated with the DARE after adjusting for the other variables.

Comparing Normative DARE to Hospital DARE

The average DARE across days for the normative NHANES sample, PICU patients, and inpatient floor patients in 3 age categories (6-9 years, 10-13 years, and 14-17 years) is shown in Table III (available at www.jpeds.com). Figure 4 displays the DARE distributions colored by age category. The trend of decreasing DARE with increasing age was observed in all groups. The average DARE in each age category and overall was significantly higher in the normative sample than both PICU and inpatient floor patients ($P < .0001$) with the greatest difference in the 6- to 9-year-old PICU patients (75% vs 59%).

Comparing Last Day of PICU with First Day on the Floor

When the unadjusted difference in DARE between the last day in the PICU and the first day on the floor were compared within subjects, we found an estimated mean increase of 2.3% DARE on the floor (95% CI 0.7%-4%; $P = .006$). After adjustment for age, sex, surgical cohort, PRISM score, log of time intubated, and race, the difference was similar (2.4%; $P = .02$).

Subset Analyses of Children >2 Years of Age

Because infants have less consolidation of activity during daytime hours than do older children, we performed a subset analysis to evaluate the DARE in children over 2 years of age ($n = 144$). The average DARE by subject was 59.7% (95% CI 58.8-60.6%) in children older than 2 years compared with 56.5% (95% CI 55.4%-57.5%) in those 2 years and under ($P < .0001$). Fifteen percent of hospital days in older children exhibited a DARE less than 50%. After adjusting for demographic variables, only PICU, cohort (orthopedic and urology), and intubation at admission were predictors of decreased DARE in children over 2 years. The highest subject DARE was 73.2%.

Discussion

The results of this study confirm that children recovering from major surgery experience disturbances in day-night activity patterns both in the PICU and after transfer to the inpatient floor setting. As the first study to

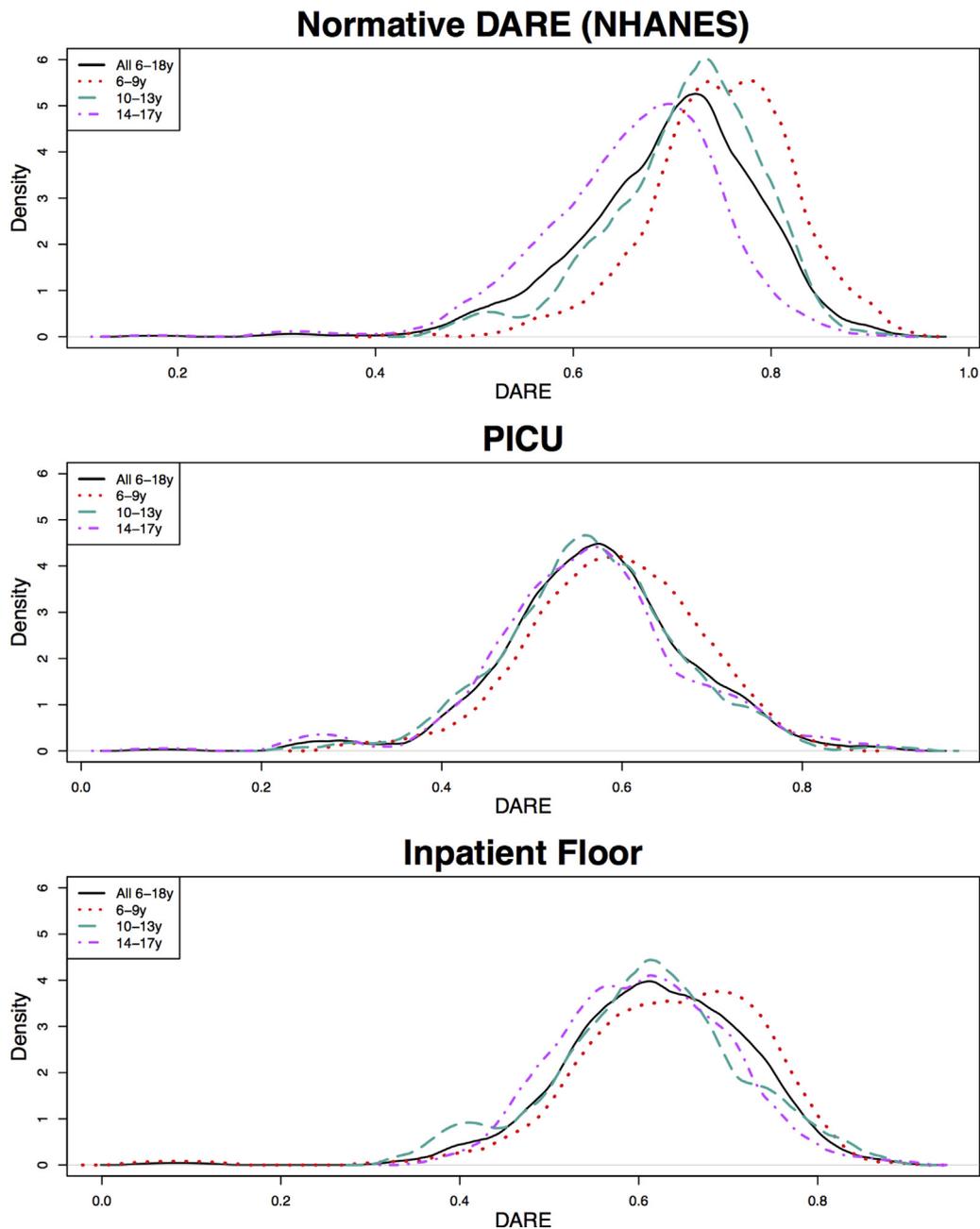


Figure 4. Comparison of normative, PICU, and inpatient floor DARE in children ages 6-17 years by age category.

characterize day-night activity patterns in a large cohort of infants and children admitted to the hospital, we also demonstrate the feasibility of actigraphy for continuous monitoring in this setting. In addition, we describe the novel application of the DARE to characterize day-night activity patterns in healthy and hospitalized children. These results provide important insights into how children's rest-activity cycles are distributed throughout the 24-hour period, suggesting that hospital setting and interventions, medications, and patient-level factors such as pain may disrupt the normal circadian rhythm after major surgery.

Our finding that, on average, only 56% of activity occurs between 8 a.m. and 8 p.m. in the PICU confirms that critically ill children have the greatest increase in the ratio of nighttime activity with absence of rest-activity cycle consolidation. These findings are consistent with those of previous studies in which actigraphy was used to measure sleep-wake patterns in hospitalized adults after major surgery. Such studies showed that total sleep time and sleep efficiency were reduced with increased awakenings.¹⁹ As shown by the normative DARE data in our analysis, even the oldest children experience disruptions in day-night activity patterns in the hospital, but this difference was most prominent in

children ages 6-9 years, a critical period of neurodevelopment. In a study of adult patients hospitalized after traumatic brain injury, rest-activity cycles were consolidated on only 46.6% of all hospital days, with a linear trend of improvement observed over time.³⁰ In the current study cohort of children without acute neurologic disease, the average DARE on the floor setting was slightly higher than that in the PICU setting, suggesting that day-night patterns do improve over time. However, it is not known whether this is a consequence of the environment, improvement in pain, or both. Although the increase in DARE (2%) between the last day in the PICU and the first day on the floor was statistically significant, a change this small is unlikely to be clinically meaningful, suggesting that the hospital setting itself, not just the PICU, is disruptive to sleep-wake homeostasis.

We found that pediatric orthopedic and urologic surgery patients have lower DARE than cardiac surgery patients, which is surprising given that cardiac surgery patients often undergo longer surgeries including use of cardiopulmonary bypass. This observation may be a reflection of neuromuscular disease and other complicating comorbidities associated with sleep disturbances in orthopedic surgery patients. Similarly, urology patients (eg, those with bladder exstrophy or hypospadias) are usually admitted to the PICU with epidurals and complex pain management including opioids and benzodiazepines to facilitate surgical healing. Opioids and benzodiazepines can be detrimental to sleep continuity and quality.⁵

Not surprisingly, duration of intubation and mechanical ventilation was associated with decreased DARE. As such, this finding implies that the effect of mechanical ventilation and/or sedation practices may have a lasting impact on sleep-wake patterns after extubation and underlines the importance of sleep promotion both during and after mechanical ventilation. Numerous studies in adults have demonstrated severe disruption in sleep architecture during invasive mechanical ventilation, including decreased rapid-eye movement sleep and slow wave sleep and loss of circadian rhythm.^{5,39,40} A cross-sectional study investigating the temporal characteristics of the sleep electroencephalogram in mechanically ventilated children found that PICU patients had more slow wave activity during daytime hours than nighttime hours, and had none of the expected ultradian variability in the electroencephalographic (EEG) power spectra.⁴¹

The current study also provides important information to support the feasibility of long-term, continuous actigraphy use in a heterogeneous population of infants and children in the inpatient setting. Actigraphy monitoring was successfully completed in 241 children from PICU admission to hospital discharge over 2333 hospital days (including intubation days). As a lower-cost and practical alternative to continuous polysomnography, actigraphy can characterize the evolution of activity patterns over time.⁴² Clinical and research applications of actigraphy to evaluate children's sleep quality in the home environment have been well-described in the literature.^{18,43-45} However, studies to evaluate activity and sleep

with actigraphy in the inpatient setting, including the ICU, have focused largely on adults.^{28-30,46-51} In a recent narrative review that covered actigraphic assessment of perioperative sleep and activity in pediatric patients, the authors included studies primarily in outpatient surgery patients.^{51,52} Our DARE data in the NHANES sample demonstrated consistency with normal sleep patterns in children, including a delayed sleep phase (later bedtime) with the onset of adolescence.⁵³ Therefore, the DARE is a useful method for objective assessment of day-night activity patterns.

The results of our study confirming disruption in day-night activity patterns highlight an opportunity for staff caring for children in the both the PICU and inpatient floor setting. Hospitals are noisy and brightly lit environments where a patient's ability to sleep is challenged by numerous disruptive factors.⁵⁴ Hospital routines are not typically coordinated to optimize sleep hygiene, as radiographs and baths are often performed during night-time or early morning hours for staff convenience in a shift-based work environment. The PICU environment can be particularly stressful for both children and their families, with monitors, alarms, and staff conversation contributing to sleep disruption in critically ill children.⁵⁵ In a recent survey of pediatric intensivists, only 16% of respondents were aware of any protocols in place for sleep promotion, such as lighting or noise reduction efforts.⁵⁶

Circadian rhythm disturbance is a risk factor for delirium, with a prevalence of approximately 25% in PICU patients.^{13,57} Pediatric delirium increases hospital length of stay and mortality.^{12,14} In addition, although pain can negatively impact sleep, sleep disruption alone can exacerbate pain and analgesic requirements.^{58,59} Sleep promotion and optimizing circadian rhythm is a noninvasive, inexpensive, and feasible approach to prevent delirium and decrease pain and analgesic needs. These interventions can be singular or multicomponent, and have been shown to improve outcomes in ICU patients.⁵⁷ In fact, the most recent update of the Society for Critical Care Medicine Pain, Agitation and Delirium guidelines has now incorporated management of sleep disruption and immobility as key components of optimizing adult ICU care.⁶⁰

This study has several limitations. First, as a single-center cohort study our findings may not be generalizable to other pediatric hospital settings. Second, we did not account for comorbidities, such as neuromuscular weakness, in assessment of the DARE. However, when used over multiple days, DARE allows the child to be his/her own reference. Third, our analysis did not consider pain, sedatives, or anesthetic medications before or during the period of actigraphic analysis, factors that may play a significant role in activity patterns and sleep quality. Fourth, age-based normative data are not available for DARE in children under 6 years of age. Therefore, we could not draw comparisons with younger patients in our inpatient cohort. However, it is likely that similar differences would be observed in younger patients. Finally, we did not have baseline data for hospitalized children for comparison. Although the difference in DARE

between the hospitalized and normative sample of children is significant, it is important to note that the 2 populations, although similar in age, could differ vastly due to other factors. NHANES aimed to gather a representative sample of the noninstitutionalized population in the US using a complex, multistage probability design.³⁶ Thus, selection bias because of possible differences in overall health status, height, weight, obese status, and other characteristics not accounted for may affect the significance of the difference in DARE between the 2 populations.

Children admitted to the PICU after major surgery experience disruptions in day-night activity patterns during their hospital stay that could reflect disturbances in circadian rhythm. Given the potential impact of circadian rhythm disturbances on the developing brain and importance of sleep during recovery from surgery, additional research is needed to identify methods of optimizing sleep hygiene and circadian rhythms in the perioperative period. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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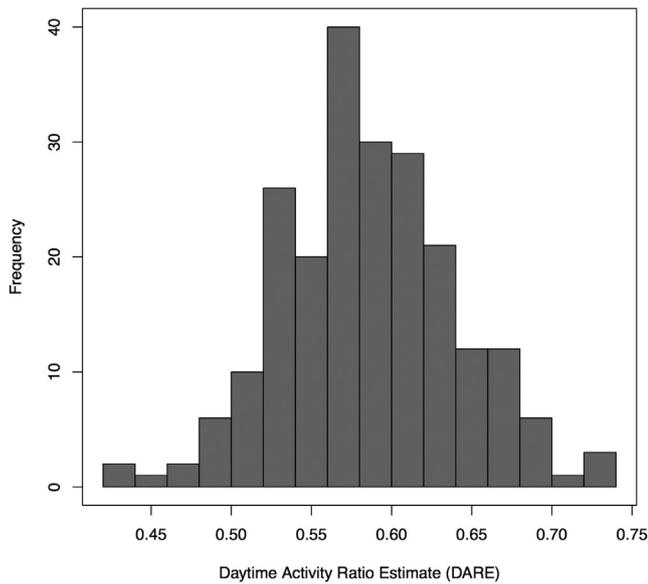


Figure 2. Histogram of average DARE by subject.

Table II. Mixed effects regression model for DARE

Variables	Coefficient	SE	T statistic	P value
PICU	-0.0530	0.0047	-11.341	<.0001
Sex (F)	0.0001	0.0067	0.086	.9931
PRISM	0.0000	0.0007	-0.047	.9628
Race				
Black	-0.0081	0.0086	-0.941	.3479
Other	0.0063	0.0081	0.775	.4390
Age	0.0018	0.0006	2.732	.0068
Cohort				
Cardiology (ref)				
Orthopedic surgery	-0.0331	0.0091	-3.627	.0004
Urology	-0.0495	0.0124	-3.977	.0001
Time intubated (log-scale)	-0.0025	0.0010	-2.569	.0109

Table III. Comparison of normative DARE vs hospitalized patients ages 6-17 years

Age groups	Number of days	Number of subjects	DARE (95% CI)
6-9 y			
Normative	264	157	75% (74.1-75.9)
PICU	117	25	59% (57.4-60.7)
Inpatient floor	117	21	63.5% (61.6-65.4)
10-13 y			
Normative	354	176	71.3% (70.5-72.1)
PICU	148	31	56.7% (55.1-58.3)
Inpatient floor	71	22	61% (58.5-63.4)
14-17 y			
Normative	504	232	66% (65.2-66.8)
PICU	230	40	56.3% (54.8-57.7)
Inpatient floor	90	29	60.7% (58.9-62.5)
All 6-17 y			
Normative	1122	565	69.8% (69.3-70.3)
PICU	495	96	57% (56.1-57.9)
Inpatient floor	278	72	58.8% (58.1-59.5)