

Is It Time to Embrace the Caffeine Level?

We thank Dr Eichenwald and the American Academy of Pediatrics for their report, "Apnea of Prematurity."¹ Working in a large 84-bed level IV NICU, we have seen firsthand the impact that an Apnea and Bradycardia Guideline can have on length of stay (LOS), parent and staff satisfaction, and other outcomes. Since we introduced our Apnea and Bradycardia Guideline 2 years ago, we have seen a reduction in our very low birth weight LOS by 24% (Vermont Oxford Network [VON] database), which we attribute in part to standardization of what we consider clinically significant events, and how we manage these events. Although the definition of apnea is not evidence based and considerable variability exists in the literature, we question the definition of an apneic spell as defined by Dr Eichenwald—cessation of breathing of >20 seconds or heart rate of <100 beats per minute when accompanied by cessation of breathing <20 seconds—because most sources define bradycardia in this situation as <80 beats per minute (and even lower at higher gestational ages). These sources also cite a minimum time period during which a bradycardic event needs to occur to be considered significant. A higher heart rate and/or lower event duration threshold may lead to unnecessary prolonged observation in the hospital for a physiologic and benign condition.

We are aware of the literature suggesting caffeine level monitoring is unnecessary because caffeine has a wide therapeutic index for the treatment of apnea of prematurity.² Our experience is that levels in the upper normal therapeutic range (15–20 mcg/mL) yield a greater response, especially for very low birth weight neonates, and that caffeine level monitoring is essential to attain these desired levels because caffeine clearance is variable. Our findings coincide with those of Dr Gal, who demonstrated a proportional caffeine

level to apnea of prematurity response relationship (even for levels 40+ mcg/mL).³ Also, some studies admit to failing to reach therapeutic levels with standard caffeine dosing, and these same studies suggest a dose-response relationship with higher levels achieving greater efficacy.² There is also evidence correlating caffeine concentration maintenance above 14.5 mcg/mL with reduced chronic lung disease rates in neonates \leq 29 weeks postmenstrual age.⁴ We continue to report chronic lung disease rates in the best VON quartile (VON database), which we attribute, in part, to maintenance of caffeine levels in the upper normal therapeutic range.

Another concern recently raised is that a significant number of infants do not have subtherapeutic caffeine levels (defined as <5 mcg/mL) 7 days after discontinuation of caffeine (the number of days often cited in the literature at which an infant can safely be discharged off caffeine), and many of these infants continue to have pathologic apnea.⁵ A benefit of obtaining caffeine levels after discontinuation of caffeine before discharge would be for calculation or estimation of patient-specific pharmacokinetic parameters to be used for prediction of subtherapeutic levels to help ensure safer discharge.⁵ We feel that this new practice will decrease the risk of patients developing postdischarge hypoxic or apneic events and possibly decrease the likelihood of readmissions for these serious events.

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Response From Committee on Fetus and Newborn

We thank Drs Kahn and Godin for their thoughtful comments on the American Academy of Pediatrics Clinical Report on Apnea of Prematurity.¹ We agree, as outlined in the clinical report, that individual NICUs should develop guidelines for monitoring of infants at risk for apnea of prematurity (including alarm limits), as well as policies and procedures for caregiver assessment, intervention, and documentation of apnea/bradycardia/desaturation events as well as the duration of the period of observation before discharge. As reported by Drs Kahn and Godin, development of such a clinical guideline regarding apnea of prematurity and its management was associated with a lower length of stay of very low birth weight infants in their NICU. Although it is difficult to attribute all of the decrease in length of stay to the apnea guideline, it does amplify the importance of consistency among providers around discharge planning for infants with apnea of prematurity.

Our definition of an apneic spell included the oft-cited duration of apnea for >20 seconds associated with

a bradycardic event of <100 beats per minute, cyanosis, or pallor. However, as we discussed in the report, most apneic events are <20 seconds because bradycardia and/or cyanosis usually occur with shorter durations of apnea. There is scant evidence for what degree, or what duration, of bradycardia should be considered clinically significant. Indeed, in infants with a postmenstrual age (PMA) <33 weeks, it is unlikely that setting of the lower heart rate alarm at <100 will influence length of stay due to recorded apnea. Our report does specify that lower heart rate alarm settings for infants with a PMA >33 to 34 weeks may be reasonable; individual NICUs are encouraged to develop these policies to provide consistency in monitoring and recording of apnea. We did not specify a specific duration of bradycardia in our report because this can be complex. For example, most clinicians would consider a bradycardic episode of 40 beats per minute to be more significant at a shorter duration than 1 of 70 beats per minute, but there are no data to inform at what duration each of these should be considered clinically significant. These decisions are best left to clinicians in the context of other medical issues in individual infants approaching discharge.

Caffeine is the preferred xanthine for treatment of apnea of prematurity, given its broad therapeutic index. The authors are correct that some infants may respond to higher doses (and

serum levels) with less apnea episodes. However, we caution that the recommended dosing regimen (20 mg/kg loading dose, and up to 10 mg/kg/day) is the only regimen that has been studied rigorously in a large population of extremely premature infants reporting both short- and long-term safety.^{2,3} In 1 recent study, infants randomized to high-dose versus standard-dose caffeine had a higher incidence of cerebellar hemorrhage and hypertonicity at term-equivalent age.⁴ These results suggest that the possible benefits of caffeine as reported in the Caffeine for Apnea of Prematurity Trial^{2,3} may not be extrapolated to higher doses, and as such, until further research is available, higher doses should be used with caution.

One advantage to caffeine is the lack of a need for routine drug-level monitoring. Our report should have specified the difference between “routine” and targeted drug-level monitoring in individual circumstances in which high or low serum levels are suspected. In addition, as Drs Kahn and Godin discuss, evidence suggests that caffeine pharmacokinetics may be different in individual infants and affected by PMA. However, not all NICUs have access to rapid turnaround of caffeine levels, which limit their clinical utility. Our report encouraged discontinuation of caffeine at the earliest possible time to avoid unnecessary delays in discharge and to await initiation of an apnea countdown for a few

days after caffeine discontinuation. There are no data to suggest this practice results in more readmissions for recurrent apnea or that routine determination of caffeine levels before starting the apnea countdown results in better outcomes. Although individual NICUs may elect to develop such a guideline, we believe it is not necessary for safe discharge of the convalescent preterm infant.

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