Neonatal Drug Concentrations – Updated November 2022

In 2011, the Institute for Safe Medication Practices (ISMP) and Vermont Oxford Network (VON) put forth recommendations, developed by a multidisciplinary working group, to standardize neonatal drug concentrations. These recommendations reflected common practices of that time, but they predated some aspects of contemporary practice. Several considerations dictated review and revision of the original recommendations.

1) Increased requirement for documented stability of compounded sterile products due to USP (United States Pharmacopeia) 797 and 800 regulations. Stability references have been located and added.
2) Changes in patterns of antibiotic use due to withdrawal of cefotaxime from the US market. Cefepime and ceftazidime are now more frequently used agents. Cefotaxime remains in the table, and cefepime and ceftazidime have been added.
3) Decreased emphasis on digoxin use in NICU. Digoxin has been removed.
4) Increased early use of caffeine citrate, particularly in extremely low gestational age (ELGAN) infants. Caffeine has been added.
5) More frequent resuscitation and ongoing care for infants weighing less than 500 grams. The 2011 ISMP/VON concentrations do not always accommodate measurable and deliverable dose volumes or rates for the smallest patients encountered in contemporary NICU practice. Dose volumes under 0.1 mL and infusion rates under 0.1 mL/hour represent the floor for dose volume or rate of infusion. Modeling the dose volume or rate for 400 g infants using usual doses and the ISMP/VON concentrations, we find several entries where dose volumes under these minimums are likely to occur.

The benefits of all hospitals using the same standard concentrations for neonates are substantial and include the following:

- Reduced medication error risk when critically ill neonates are transferred from one facility to another
- Allows development of standardized infusion device drug libraries
- Supplies the demand necessary for manufacturers to offer commercially prepared products when not already available.
- Reduced risk of extemporaneous compounding errors within hospitals.

We urge all hospitals that treat neonatal patients to consider adopting standard drug concentrations, and to anticipate and accommodate the smallest patients and the multidisciplinary team caring for them. We modeled dose and dose volume across the range of NICU patients, 400-5000 g. Our goals were measurable volumes and rates, and avoidance of excessive fluid from medications. Concentrations of known stability are offered. Concentrations that are a ten-fold difference are avoided. When possible, the same concentration will work for both NICU and pediatric patients who are small enough to receive drug infusions via syringe pump, rather than as minibags, which has error prevention and economic advantages for pharmacy practice.

The information in this document was reviewed by Kelly Burch, PharmD, BCPPS, Julie Choudhury, PharmD, and K. Suresh Gautham, MD, DM, MS, FAAP and published in November, 2022 on the Vermont Oxford Network website (URL:).

Table 1: Concentration recommendations for NICU patients <u>weighing 500 g or more</u>. These recommendations also apply to pediatric patients receiving medications via syringe pump.

Drug	Intermittent (I) or Continuous (C)	Concentration	Units	Stability reference *	Comment/controversy/query
acyclovir	I	7	mg/ml	1	
alprostadil	C	10	mcg/mL	1	
amphotericin B	I	0.1	mg/mL	2	
amphotericin B liposomal	I	1	mg/mL	1	
ampicillin See footnote #	I	30	mg/mL	1	Pharmacy compounded
ampicillin	I	100	mg/mL	1	Bedside compounded
caffeine citrate	I	20	mg/mL	1	
cefazolin	I	100	mg/mL	1	
cefepime	I	100	mg/mL	1	
cefotaxime	I	100	mg/mL	1	Cefotaxime is currently not available in the US. International colleagues continue to use this agent.
ceftazidime	I	100	mg/mL	1	
clindamycin	I	6	mg/mL	3	
dobutamine	C	2000	mcg/mL	3	Dobutamine 2000 mcg/mL does not result in measurable rates for patients under 500 g.
dopamine	C	1600	mcg/mL	3,4,5	Dopamine 1600 mcg/mL does not result in measurable rates for patients under 500 g.
epinephrine	C	10	mcg/mL	1,5	Epinephrine 10 mcg/mL does not result in measurable rates for patients under 500 g.
fentanyl	I	10	mcg/mL	8	Fentanyl 10 mcg/mL does not result in measurable dose volumes for patients under 500 g.
fentanyl	C	10	mcg/mL	8	Fentanyl 10 mcg/mL does not result in measurable rates for patients under 500 g.
fluconazole	I	2	mg/mL	3	
furosemide	I	10	mg/mL	3,9	
furosemide	C	10	mg/mL	3,9	
gentamicin	I	10	mg/mL	3	Gentamicin 10 mg/mL does not result in measurable dose volumes if low doses (2.5 mg/kg) are used. If doses of 5 mg/kg are used, 10 mg/mL results in measurable dose volumes, which can be delivered using contemporary infusion equipment.
heparin in 0.45% NaCl	C	0.5	unit/mL	1, 11	
insulin	C	0.5	unit/mL	12,13	Insulin 0.5 units/mL does not result in measurable rates in patients under 500 g.

metronidazole	I	5	mg/mL	3	
midazolam	I	1	mg/mL	3, 14	Midazolam 1 mg/mL does not result in measurable dose volumes in patients under 500 g. Midazolam 0.2 mg/mL is recommended to avoid a 10 x dilution, and to avoid confusion with morphine 0.1 mg/mL.
midazolam	C	1	mg/mL	3, 14	Midazolam 1 mg/mL does not result in measurable rates. Midazolam 0.2 mg/mL is recommended to avoid a 10 x dilution and confusion with morphine 0.1 mg/mL.
morphine	I	0.5	mg/mL	15,16	Morphine 0.5 mg/mL does not result in measurable dose volumes in patients under 500 g.
morphine	C	0.5	mg/mL	15,16	Morphine 0.5 mg/mL does not result in measurable rates in patients under 500 g.
norepinephrine	C	16	mcg/mL	1	Norepinephrine 16 mcg/mL does not result in measurable rates in patients under 500 g.
phenobarbital	I	10	mg/mL	18	
	I	65	mg/mL	3	Phenobarbital 65 mg/mL does not result in measurable dose volumes for maintenance doses. Consider 10 mg/mL.
vancomycin	I	5	mg/mL	1	

* Stability for some of the recommended concentrations is extrapolated using the concept of “bracketing”. Data on stability at concentrations lower and higher than the desired concentration can be applied to the desired concentration. For example, if gentamicin 1 mg/mL and 10 mg/mL are known to be stable in solution, then admixtures of 2 mg/mL are supported. (https://www.fda.gov/media/71720/download)

Ampicillin stability changes across the range of practical concentrations which complicates these recommendations. Although 100 mg/mL ampicillin is only stable for a brief time, we recommend using 100 mg/mL when doses are compounded from dry powder at the bedside. This is also useful for emergency departments. ASHP S4S intends to recommend 20 mg/mL for pediatric patients. There are advantages to 20 mg/mL over 30 mg/mL: the familiarity of compounding "1 gram in 50 mL"; dividing the desired dose by 20 rather than 30 may give an easier to deal with dose volume; 20 mg/mL has longer stability than 30 mg/mL. The disadvantage is fluid volume of 2.5-5 mL/kg, which may be given IV push. ASHP recognizes the problem this represents for NICU patients. Thus, ASHP will probably recommend 30 mg/kg for NICU.

Table 2: Concentration recommendations for NICU patients <u>weighing less than 500 g</u>. Organizations where care is provided (or anticipated) for patients weighing less than 500 g should consider prospective technology built around these concentrations, aligning the EHR, compounding software and tools, and smart pump libraries.

Drug	Intermittent (I) or Continuous (C)	Concentration	Units	Stability reference *	Comment/controversy/query
dobutamine (less than 500 g current weight)	C	1000	mcg/mL	3	Consider if care for patients under 500 g is anticipated.
dopamine (less than 500 g current weight)	C	800	mcg/mL	3,4,5	Consider if care for patients under 500 g BW is anticipated.
epinephrine (less than 500 g current weight)	C	5	mcg/mL	1,5	Consider if care for patients under 500 g BW is anticipated.
fentanyl (less than 500 g current weight)	I	2	mcg/mL	6,7	Consider if care for patients under 500 g is anticipated and fentanyl is the preferred opioid analgesic agent.
fentanyl (less than 500 g current weight	C	2	mcg/mL	6,7,8	Consider if care for patients under 500 g is anticipated and fentanyl is the preferred opioid analgesic agent.
furosemide (less than 500 g current weight)	I	2	mg/mL	9	Consider if care for patients under 500 g is anticipated.
gentamicin (less than 500 g current weight)	I	2	mg/mL	10	Consider if care for patients under 500 g is anticipated and dosing protocols include low doses.
insulin (less than 500 g current weight)	C	0.1	unit/mL	12,13	Consider if care for patients under 500 g is anticipated.
midazolam (less than 500 g current weight)	I	0.2	mg/ml	14	Consider if care for patients under 500 g is anticipated. Midazolam 0.2 mg/mL is recommended to avoid a 10 x dilution and confusion with morphine 0.1 mg/mL.
midazolam (less than 500 g current weight)	C	0.2	mg/ml	14	Consider if care for patients under 500 g is anticipated. Midazolam 0.2 mg/mL is recommended to avoid a 10 x dilution and confusion with morphine 0.1 mg/mL.
morphine (less than 500 g current weight)	I	0.1	mg/mL	15,16	Consider if care for patients under 500 g is anticipated and morphine is the preferred opioid analgesic agent.
morphine (less than 500 g current weight)	C	0.1	mg/mL	14,16	Consider if care for patients under 500 g is anticipated and morphine is the preferred opioid analgesic agent.
norepinephrine (less than 500 g current weight)	C	4	mcg/mL	1, 17	Consider if care for patients under 500 g is anticipated and norepinephrine is part of practice.

* Stability for some of the recommended concentrations is extrapolated using the concept of “bracketing”. Data on stability at concentrations lower and higher than the desired concentration can be applied to the desired concentration. For example, if gentamicin 1 mg/mL and 10 mg/mL are known to be stable in solution, then admixtures of 2 mg/mL are supported. (https://www.fda.gov/media/71720/download)

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