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The conundrum of off-label and unlicensed drug usage in neonatology

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"The challenge of safe and appropriate use of drugs in the neonatal period is a daunting one and is complicated by the glaring lack of evidence-based data that should guide decision making. Clinicians struggle with a meager choice of drugs that have not been rigorously tested in the tiniest newborns; they often complicate this issue with their own unacceptably high variation in drug usage, which precludes collection of meaningful outcomes data. The result is an unsatisfactory state of either too much or too little use of drugs, and an industry that has yet to embrace pediatric drug development as an essential part of their overall strategy. Newborns worldwide continue to suffer with plenty of blame to be passed around and few ready to shoulder the responsibility."[1]

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In a recent editorial,[2] The New York Times talks about the many advances in neonatal care in the last few decades and how they have impacted mortality amongst the most vulnerable neonates. "In the 1960s, when the first neonatal intensive care units (NICUs) opened, premature infants had a 95% chance of dying. Today, they have a 95% chance of survival."[2] No doubt, these gains have come from relentless efforts by scientists in closing the knowledge gap and by clinicians who focused on the implementation gap. Laboratory observations, such as the one showing the maturational effect of antenatal steroids in lung development,[3] were tested in large randomized controlled trials and put into clinical practice by clinicians,[4] albeit often at a slow pace. However, antenatal steroids, whose efficacy and safety has now been demonstrated in numerous other trials and metanalyses,[5] are still not approved for use in preterm pregnancies; as such, their use in millions of pregnant women worldwide would be considered "off-label" use.[6] Yet other discoveries, such as the observation of the lack of bubbles in airways of preterm animals with lung disease, led to rapid development and application of commercial surfactants approved for their specific use in neonates.[7]

There are estimates that as much as 40 to 80% of drug usage in the NICU is off-label or unlicensed[8]; this is particularly important given the large number of prescription drugs that are administered to hospitalized neonates. In this issue of the Jornal de Pediatria, Carvalho et al.[9] report results of a prospective observational cohort study conducted in Brazil evaluating the use of off-label and unlicensed drugs in the NICU. Their results confirm what previous studies from other countries have also shown: very few patients (21%) receiving medications in the NICU meet the requirements for appropriate use. A good number of patients received off-label and unlicensed medications, including commonly used drugs such as caffeine, cefotaxime and dexamethasone. The study also evaluated daily Neonatal Therapeutic Intervention Scoring System (NTISS) scores and their relationship with inappropriate drug usage. Authors report a higher prevalence of off-label use of drugs in preterm infants < 35 weeks and in those with higher NTISS scores. As expected, there was a

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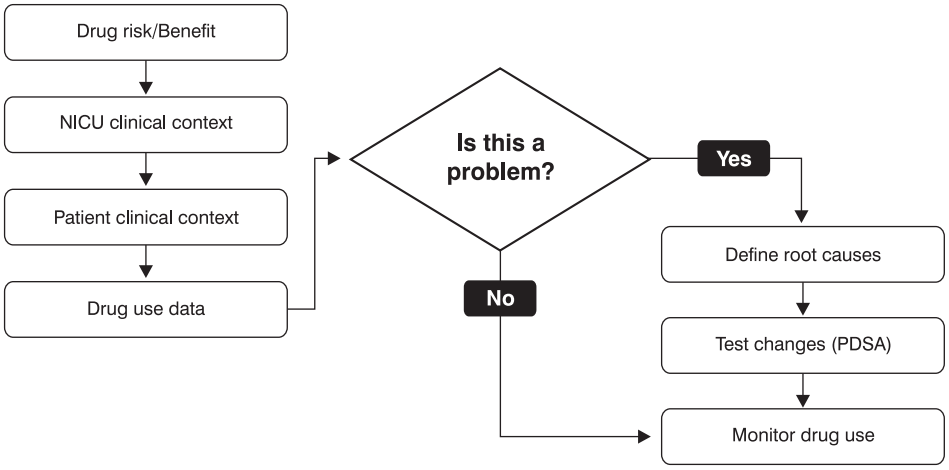
direct relationship between NTISS scores and the number of unlicensed and off-label prescriptions. However, there was also an inverse relationship between gestational age and the overall number of prescribed drugs, since many of the above mentioned neonates were sicker. Authors failed to report any interaction between gestational age and NTISS scores; it is conceivable that the reported relationship between high NTISS scores and high usage of off-label medications is primarily due to the underlying immaturity. If this was the case, then stratification by gestational age would be necessary.

These issues notwithstanding, authors substantiate a high prevalence of unlicensed and off-label drug use in neonates. This is cause for concern since many of these medications have the potential to do more harm than good. Clinicians have an obligation to "first do no harm" by avoiding inappropriate use of medications. Medications used to manage gastro-esophageal reflux are great examples of agents that have no documented benefit but significant safety issues.[10] Similarly, many drugs used in neonatal resuscitation are seldom needed.[11] Most neonatologists will also acknowledge that antibiotics are among the most abused drugs in the NICU, with great variability in treatment protocols.

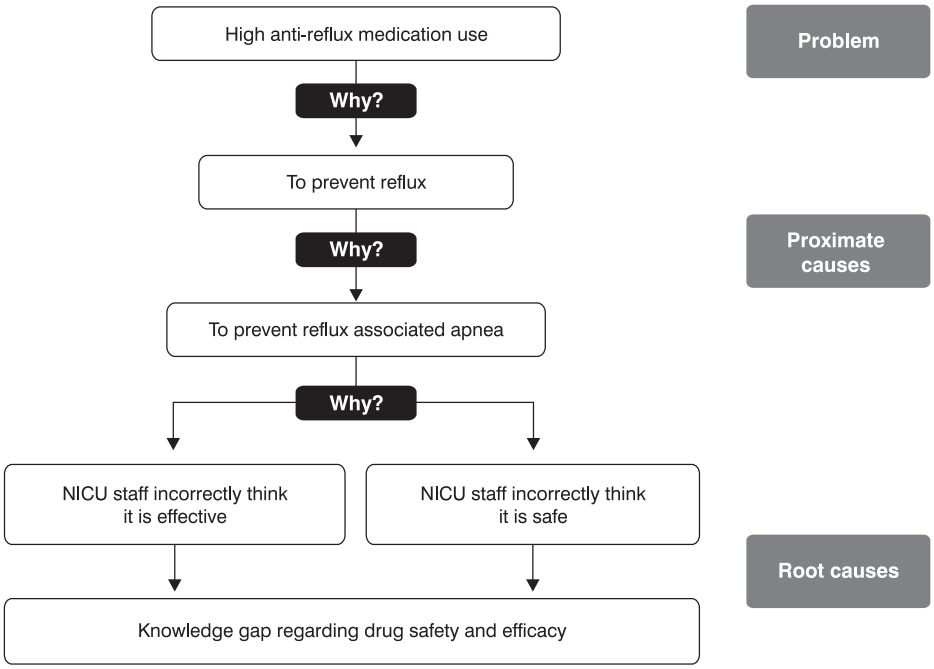
So where does this leave us and how does the busy clinician manage medication use in a NICU as we move forward? While new drugs may change practice, it is incumbent upon us to begin with better use of existing drugs. In a recent article, Drs. Ellsbury and Ursprung provide us with a useful framework for optimizing medication use in the NICU.[12] Figures 1 and 2 show time-tested quality improvement approaches to drug usage. These approaches allow for adaptation of drugs used to the specific clinical situations faced in the NICU, with an eye towards minimizing harm. Figure 2 emphasizes the use of root cause analysis and team approach to make a decision about medications such as antireflux drugs in the NICU.

Finally, it is clear that the pharmaceutical industry and funding agencies have a moral obligation to perform drug studies in newborns. Clearly, off-label use of drugs in newborns worldwide is in large part a reflection of the lack of clinical trials in neonates, forcing practitioners to extrapolate from studies performed in older children and adults. There are many factors that impede the development of newborn drug studies[8]; these argue for special financial incentives for companies that invest in drugs for neonatal use, and special funding mechanisms from funding agencies such as the National Institutes of Health for neonatal drug trials. They also call for a renewed partnership between the academic institutions and industry to promote neonatal drug trials. The history of our young subspecialty is replete with examples of creative thinking and scientific advances; there is no reason why we should feel left behind on this important issue of medication stewardship.



NICU = neonatal intensive care unit; PDSA = Plan-do-study-act.
Adapted (with permission) from Ellsbury & Ursprung.[12]

Figure 1 - Quality improvement approach to optimizing drug use



NICU = neonatal intensive care unit.
Adapted (with permission) from Ellsbury & Ursprung.[12]

Figure 2 - Root cause analysis applied to the use of antireflux medications in the neonatal intensive care unit

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