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EDITORIAL

History of Neonatal Medicine—Limitations in Studies, Guidelines, and Resources Impact Progress

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The two-part historical review of neonatal medicine published by Drs. Lussky, Cifuentes, and Siddappa is an excellent overview of the challenges and triumphs of neonatal medicine over more than a century of advances.[1,2] The authors document well-known examples of advances as well as some of the biggest therapeutic misadventures in neonatal medicine. The authors' advocacy for changes in social policy is equally important: the health of the intra-uterine environment has profound impact on both short- and long-term outcomes, and may be the source of undesirable outcomes erroneously attributed to the practice of neonatal medicine. The current reviews,[1,2] as well as other excellent reviews by experts much admired for their expertise and sustained contributions to neonatal medicine,[3,4] tend to be critical of the failure to adhere to evidence-based medical practice. The tendency has often been to extrapolate scientific rationale attributed to animal studies or adult diseases with similar pathophysiology to the care of neonates. Conversely, this may be too critical a perspective given the controversy and disagreement among experts that prevail in many areas of medicine.

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There is an alternative perspective—that evidence-based practice, difficult to apply in neonatal medicine, will remain so as long as there is a dependency on small studies. These studies are too often grouped into meta-analyses despite having considerable methodological differences and conflicting outcomes. Consequently, few absolute statements about best practices can be made. In our experience of over two decades in neonatal medicine, the pendulum of practice change tends to swing too far in one direction or is suddenly reversed when such studies raise something short of definitive concern with current practice. Consider for example the recent multicenter trial of the early initiation of hydrocortisone to prevent bronchopulmonary dysplasia (BPD).[5] The findings suggest that patients exposed to chorioamnionitis are the ones who benefit. The BPD-prevention benefits are not seen when chorioamnionitis is absent. This same study was stopped prematurely because of an apparently excessive risk of gastrointestinal perforation and hemorrhage when hydrocortisone was used concurrently with indomethacin. Based on this evidence, one might conclude that hydrocortisone and indomethacin should not be used concurrently and that the risk of excessive toxicity might justify avoiding future use of hydrocortisone. The problem is that

ABBREVIATIONS: BPD, bronchopulmonary dysplasia; EEG, electroencephalogram

such large trials represent but one therapeutic strategy and often one permutation of several possible ways to use that strategy. We have routinely used concurrent ranitidine for gastrointestinal prophylaxis when using steroids and have rarely observed gastrointestinal bleeding or perforation. Similarly, the early use of dexamethasone is associated with subsequent neurodevelopmental problems, but later use and different steroids may not have the same association. Thus, what might be viewed as a therapeutic misadventure by some (i.e., the use of postnatal steroids) might be viewed another way if a slightly different therapeutic strategy were implemented.

When treating the critically ill, the immediate need to improve endpoints of treatment that most acutely threaten a patient's well being makes the most intuitive sense. In the case of therapeutic interventions, this involves weighing the available guidelines, case reports, extrapolation from adult clinical trials, and other data sources. This requires a close collaboration of physicians, pharmacists, and others to bring all perspectives to the table. Irrespective of whether one practices in primary care neonatology or practices in an academic research center, both face frequent decisions on the "best clinical practice" for a critically ill patient. In each case, the neonatology team must weigh whether that specific patient should receive a potentially risky treatment or should receive plateau care with monitoring of the natural course of the disease and its complications. Surveys demonstrate that different clinicians choose to consider the risks differently,[6] resulting in an acceptable range of practice variability.[7]

As with many other fields of medicine, mistakes in the use of selected therapies have resulted in patient harm rather than benefit. This is further complicated in the case of neonates because, with a few exceptions, investment in researching therapeutic options for this group is quite limited, and studies often report results using small patient numbers. Long-term neurodevelopmental studies are often unavailable, and timing of therapies such as systemic steroids may provide different outcomes, so a drug therapy cannot be considered without the context of timing, different dosing strategies, and different drugs in the same pharmacologic category. An additional problem is that not all neonatal units have the same resources to monitor treatment endpoints. For example, in a recent informal survey of seizure management in neonates, it was apparent that most centers still use clinical presentation of seizures to provoke inclusion of an electroencephalogram (EEG) and/or subspecialty consultation to evaluate seizures. Furthermore, seizure response is primarily gauged based on clinical grounds, rather than confirmatory EEG. These approaches occur despite data showing that electrographic seizures often occur without clinical equivalents and that even with treatment using phenobarbital or phenytoin, electroclinical dissociation occurs in up to half the patients. Data also show that ongoing electrical seizure activity may be harmful. The reason that practice has often not caught up with evidence is in part a resource problem. Many centers lack video-EEG equipment while others lack sufficient pediatric neurologist expertise to support the volume of video-EEG information that would be generated.[8] The potential hazards of continuing to use clinical endpoints cannot be known unless adequate clinical trials are performed, but real-world considerations force most centers to continue the current practice. With so many confounding considerations, it is hard to realistically balance risks and benefits. Given the difficulty of knowing what is best practice and the resource limitations confronting those caring for newborns, clinicians working in neonatology should not judge themselves or others too harshly when a therapy selected in the best judgment of the physician has a suboptimal result. We should all try to apply evidence-based medicine to our practice, but the strength of that evidence should be weighed carefully before accepting it, even from a seeming authoritative source. Future studies should continue to use a collaborative multicenter approach, but not limit participants to academic centers. There are many regional community level III centers with as many admissions as in these academic "meccas", and the valuable information they can provide is amply demonstrated in the publications from the Vermont-Oxford network. The value of regional or state-wide population-based outcomes cannot be overlooked in terms of value. Lastly, a multidisciplinary ap-

proach to best practices development should be implemented utilizing the perspectives of physicians, pharmacists, nurses, nutritionists, respiratory therapists, and hospital administrators responsible for allocation of resources. Otherwise guidelines will be made in an academic vacuum, reflecting the current state in which guidelines trickle down poorly to a broad range of neonatal practice sites.

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