Determining the Optimal Neonatal Care for Preterm Infants in the Era of Personalized Medicine

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The results of the Tor2rpido study[1] illustrate the challenges of identifying optimal treatments and care processes for patients in the era of personalized medicine. This study investigated an important area: the initial management of oxygen during the resuscitation of an infant. Oxygen delivery has changed from beginning at high oxygen concentrations to much lower concentrations and, in both cases, titrating the oxygen to the response of the infant. These policies stem from studies of term infants, which found improved outcomes and lower markers of oxidative stress in infants who received much lower oxygen concentrations to begin their resuscitation.[2,3] These results are frequently applied to the resuscitation of prematurely born infants, even though the studies in this patient population provided less consistent results.[4–6] Similar to a population-based study from Canada,[4] the results of the Tor2rpido study suggest that, in a subgroup of prematurely born infants, resuscitations that start with room air may be harmful. But which infants are they, and how could we identify infants for whom their initial physiology required a different process of care than infants born at term gestation?

This question highlights the heterogeneity of treatment responses that seemingly occurs for every therapy.[7,8] Standard clinical trials, which divide a group of patients by using a random allocation to receive either a treatment or a control treatment in parallel, identify the average treatment effect when applied to a population. When administered to a specific patient, however, this treatment may provide even greater benefit, or harm, depending on specific patient characteristics. This finding is part of the growing awareness of "personalized medicine." Best illustrated in oncology, personalized medicine operates under the theory that multiple factors influence how a patient responds to a specific treatment, allowing for a tailored approach to treatment.[9] Although it is common for many oncology patients to receive therapies tailored to their specific characteristics, such personalization of treatment is much less common in other areas of pediatrics, such as neonatal care.

How should clinicians and scientists reconcile the inherent conflict between standard clinical trial methodology and personalized medicine practices? Ideally, before undertaking a therapeutic trial, we would understand the underlying biology of the process well enough to identify potential responders to the proposed therapy and then primarily study those patients. Probably more importantly, we should be able to identify those patients potentially at risk for harm when given the treatment. Unfortunately, we usually do not have the requisite knowledge about the underlying biology or genomics of the disease to identify such responders and nonresponders. In addition, many personalized medicine studies

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focus primarily on the genetics of the disease, ignoring other factors that may modify the outcome of a treatment, such as a patient's physical or social environment, which may have a tremendous influence on chronic diseases such as asthma; the fetal environment; or the widely variable clinical manifestations of diseases such as asthma or bronchopulmonary dysplasia.

The Tor2rpido study[1] illustrates 1 potential solution to this issue: defining a priori subgroups within the initial clinical trial design to allow for appropriate sampling of these groups through stratified randomized practices. A priori subgroups, however, require the following: (1) the knowledge that these subgroups may respond differently to the treatment; (2) the inability to recruit patients within these subgroups, especially for low-incidence diseases such as the extremely premature infant; and (3) the ability to study few subgroups because of sample size constraints. There are other innovative methods that have been underused in the pediatric and neonatal literature:

Improvements in personalized randomized controlled trials, also known as N-of-1 trials.[8] N-of-1 trials randomize an individual to periods of time receiving either a treatment or a control intervention, monitoring responses to each intervention to understand a patient's response to a treatment. These studies allow for both the testing of a given set of treatments on a given patient and the explicit measurement of the heterogeneity of treatment effects when multiple N-of-1 studies are combined. There have been few uses of N-of-1 studies in the pediatric literature. Reviews of the adult literature find variable study designs and reporting[10–12] that should improve with recently published Consolidated Standards of Reporting Trials guidelines regarding N-of-1 studies.[13]

New causal inference methods for observational data. The growing availability of big data sets, which include clinical and mechanistic information, allow for the examination of many modifiers of treatment effects. Although observational in nature, the growing application of such methods in pediatrics, such as propensity scores and instrumental variables approaches, provide stronger evidence of a causal link between treatment and outcome than traditional regression-based methods.

With the application of these innovative methodologies, clinicians will have new information to help determine the ideal processes of care to give a specific patient, optimizing their outcomes of care.

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