Commentary

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Where do we stand in the field of neonatal jaundice? Commentary on the 2017 J. Donald Ostrow Trieste Yellow Retreat

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In early September 2017, a small but dedicated group of researchers in the field of neonatal jaundice gathered in Trieste, Italy, with the goal of highlighting the latest research advances and encouraging future collaborations. The 2-day biennial J. Donald Ostrow Yellow Retreat (DOTYR, **Figure 1**) was organized by the Italian Liver Foundation (FIF) and it included members of the neonatal jaundice research community, representing 22 institutions and 12 nations. The research presented at the 2017 DOTYR showed that the current understanding of neonatal hyperbilirubinemia and the associated therapies requires more detailed study and will likely require revision in the future. The present commentary will summarize the most pressing concerns addressed at the 2017 DOTYR and will discuss directions for possible future research.

Neonatal jaundice is a common condition, with 60–80% of newborns classified as jaundiced. Considerable effort goes into screening and treatment (phototherapy (PT) or exchange transfusion) to prevent this condition from escalating into the development of brain damage and its resulting sequelae, known as kernicterus. Kernicterus is classically recognized as varying degrees of auditory and motor dysfunction occasionally associated with oculomotor dysfunction and dental staining. Although it is not disputed that the source of brain damage in kernicterus is elevated unbound "free" bilirubin depositing into the brain during extreme jaundice, numerous questions still remain about the condition. Notable questions include the following: What is the worldwide prevalence of the disease? What is the mechanism of bilirubin neurotoxicity? What role do genetics play in resistance to bilirubin neurotoxicity? Can patient screening be improved? Are there any unintended side effects of PT? Do current treatment guidelines for exchange transfusion need to be re-examined?

Figure 1. J. Donald Ostrow Yellow Retreat official logo.

UNDERESTIMATION OF THE REAL INCIDENCE OF NEUROLOGICAL SEQUELAE IN SEVERE HYPERBILIRUBINEMIA, AND THE NEED FOR IMPROVED RISK ASSESSMENT

(1) The implementation of protocols and procedures to address severe neonatal jaundice and prevent kernicterus has been successful in the industrialized world. Unfortunately, this success has led to the false belief that kernicterus is no longer a concern. Indications are clear that severe jaundice and negative neurological outcomes are an ongoing problem in developing countries, where access to proper monitoring and treatment can be lacking.

(2) The use of multiple terms to describe kernicterus, including chronic bilirubin encephalopathy, bilirubin-induced neurological disorder (BIND), and the narrow definition of severe kernicterus, has led to confusion among both families and clinicians. Moreover, it has led to a significant underestimation of the number of children and adults who suffer from neurological disorders resulting from perinatal exposure to bilirubin but are not recognized as having a form of kernicterus due to the mildness of their symptoms. A proposal to modify the current terminology used in the field of neonatal jaundice to describe kernicterus emerged from the conference. Participants proposed that the currently used terms be replaced by the new term kernicterus spectrum disorder (KSD), which includes mild, moderate, and severe kernicterus under a single label (1).

(3) In addition to talks investigating the neurotoxic effects of bilirubin, a number of presentations examined the

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protective effects of mild bilirubin in the body. It has been recognized that bilirubin has important natural antioxidant and immunomodulatory properties (4,5), which may explain why most children experience an increase in bilirubin levels shortly after birth, and why patients with Gilbert syndrome present a lower incidence of chronic pro-oxidant and proinflammatory pathologies (e.g., metabolic syndromes). Because of the relevant benefits of having a low-to-moderate TSB, modulating bilirubin metabolism in order to use the yellow pigment as a therapeutic molecule remains an attractive avenue for future research.

(4) Total serum bilirubin (TSB) levels are used as a proxy for measuring unconjugated, unbound, or "free" bilirubin (Bf, the recognized neurotoxic form of bilirubin (2)), because of the difficulty in performing this measurement in clinical settings. Clinical Bf measurement remains a need, not only to reduce the number of children, especially those born premature, who may develop kernicterus, but also to reduce the unnecessary treatment of children with exchange transfusion (ET) or PT. With that need in mind, the latest updates on a novel probe for Bf were presented at the 2017 DOTYR. The new probe, bound to an infrared fluorophore, is designed to be used with as little as 5 µl of whole blood. The use of this probe for clinical Bf testing will be possible through the use of a system composed of a custom chip containing the probe that is measured with a small reader at the bedside. This system will allow physicians to address the clearly demonstrated bias of estimating Bf from TSB and serum albumin level. It will also allow for the possibility to address drug interferences with albumin–bilirubin binding. When this new Bf probe system receives approval for use in the United States, it has the potential to markedly alter the care of jaundiced children for the better.

(5) The current level of knowledge about the genetics of kernicterus is inadequate or significantly incomplete. The possibility was also presented that an individual's genetic background influences the susceptibility to develop a KSD. Bench-side studies and association studies (e.g., the reported association between galactosemia and KSD), as well as new technological approaches, are needed. The pathway genetic load (PGL) score has been proposed as a novel and targeted-analysis approach that is based on the hypothesis that a combination of mildly deleterious single-nucleotide polymorphisms can create an "at-risk" state in newborns exposed to severe hyperbilirubinemia. PGL ((3)—clinical trials ongoing) requires fewer samples than a traditional genome-wide association study and identifies significant mutation patterns that would otherwise be overlooked. If successful, this approach would potentially allow for the creation of a simple genetic-screening assay of jaundiced infants to determine the genetic predisposition to bilirubin neurotoxicity, improving the selectivity of who needs and who does not need advanced treatment for jaundice.

ADDRESSING THE NEED FOR IMPROVED THERAPEUTIC OPTIONS

(1) A warning has been raised on the erroneous confidence in the current "dogmas" relating to the actual therapy efficacy and safety of PT and "immediate" exchange transfusion. PT has been reported as inducing inflammation and DNA damage (especially during intermittent PT vs. continuous PT). Newborns with severe jaundice who are not responding to PT are thought to need immediate exchange transfusion. Because of the exchange needing to be "immediate", they are treated with emergency-released packed red blood cells instead of matched, washed blood in an effort to reduce the time to transfusion. This treatment leads to a decline in serum albumin, because of its reduced plasma content, limiting the ability of the transfused blood to bind any remaining bilirubin. At the DOTYR, it was recommended to begin the washing and cross-matching of blood as soon as a child is placed under PT, so that the more efficacious blood will be ready for a transfusion if the PT proves unsuccessful.

(2) From the above reports, it is clear that there is a need to develop novel treatment strategies. To that end, lessons from other neonatal pathologies must be considered. As hypothermia is an accepted treatment for other diseases in children, such as hypoxic ischemia, and experimental evidence indicates that hypothermia reduces neuronal cell death during hyperbilirubinemia, clinical trials for this treatment in severely jaundiced infants would be feasible to pursue immediately. In addition, efforts should not be discontinued to improve neonatal care through research into molecular effectors of bilirubin toxicity that could be used as therapeutic targets. New developments continue to emerge on this front, such as the observation that bilirubin binds to lipid rafts in the membranes of cerebral granule neurons, disrupting the rafts and neurite outgrowth signaling through the L1 cell adhesion molecule. Notably, this mechanism of toxicity is blocked by administration of choline.

SUMMARY

In summary, the DOTYR provided a valuable collegial forum to review the current state of research regarding neonatal jaundice and hyperbilirubinemia in general. From the presentation of new therapies and new terminology to the reassessment of current therapies and entrenched ideas, much work has been conducted to address the many unanswered questions in this field. We expect to see significant progress in the field for the years to come as the research community continues to grow and develop.

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