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SPECIAL ARTICLE

# Commentary on the Don Ostrow Trieste Yellow Retreat 2019: a successful biennium, what next?

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## INTRODUCTION

The biennial 2019 Don Ostrow Yellow Retreat (DOTYR) in Trieste, Italy is a meeting of about 100 international participants representing the small but dedicated group of researchers working towards a better understanding of both the positive and negative clinical functions of bilirubin (Fig. 1). This 2-day retreat was organized by the Italian Liver Foundation (FIF). The retreat was divided into five topic sessions that included basic, clinical, and translational science research (detailed information on the topics and presentation may be found online at https://www.fegato.it/fondazione-italiana-fegato.html). In this commentary, we will be giving our impressions of the current state of the field of bilirubin research as well as thoughts of where it may be headed.

## A LONG-AWAITED STEP FORWARD—BEDSIDE-FREE BILIRUBIN (BF)

Neonatal hyperbilirubinemia is a common occurrence in newborns with a small percentage of those experiencing extremely high, pathological levels of bilirubin. Left untreated severe hyperbilirubinemia leads to brain damage known as kernicterus spectrum disorder (KSD). Numerous articles and reviews have argued that the classic measure of bilirubin in the body, total serum bilirubin (TSB), is only an indirect measure of the more reliable correlation to toxicity, unbound bilirubin (Bf).[1] While the use of the "Peroxidase Method", first described in the 1970s, can successfully measure Bf in the blood,[2,3] due to technical hurdles, automation of this method for clinical use has never been implemented outside of Japan. Therefore, we are pleased to see that the production of a reliable point-of-care Bf reader continues to progress. This novel Bf reader requires only 5 µl of whole blood to produce a concentration in around 60 s. Interestingly, it was reported that phototherapy (PT) is effective in decreasing TSB (as expected by decades of experience), but this decrease does not coincide with an equivalent decrease in Bf. Based on observations of Bf concentrations, infants are overtreated with PT. These data suggest possibly reducing UV exposure and promoting extended hospitalization. It was shocking to hear that among 40 drugs typically used in newborns, nearly a quarter (22%) of these drugs showed a displacing effect, increasing Bf anywhere from 80 to 1600%. A similar effect was also documented for intra-lipids, frequently administrated especially to preterm infants.

For some time now, Bf has been the demonstrated indicator for neurological damage, and the inability for the traditional TSB measurement to account for the effects of bilirubin displacing drugs makes it even more unreliable than previously thought. The development and implementation of a true point-of-care Bf measurement device would not only be expected to reduce the number of cases of kernicterus but also allow for a safe reduction in the number of unnecessary and possibly dangerous PT. However, to make the measurement of Bf a routine test, a massive global effort is now required for the approval and implementation of these devices. This effort will begin with clinical studies of efficacy in each region before new guidelines for intervention can be written and implemented.

## THE CURRENT WORLDWIDE SITUATION

While we wait for the implementation of clinical Bf quantification worldwide, the DOTYR 2019 stressed the importance of a "comprehensive approach" (recognizing icterus—quantify TSB—apply efficient therapy) to neonatal hyperbilirubinemia.

It should be acknowledged that there has been great success in the overall reduction of severe KSD through the use of various TSB quantification point-of-care devices.[4] Nevertheless, the DOTYR highlighted the lack of reliable numbers for the prevalence of severe neonatal jaundice and reemphasized the fact that (1) severe neonatal jaundice continues to be a challenge everywhere, and (2) that each region has its own unique set of challenges. Thus, it was not surprising to see that the development of local treatment guidelines is a requirement for successful neonatal management. Despite that, the DOTYR 2019 participants agreed that the major obstacles in preventing mild to severe KSD share some commonalities: first, the ignorance to—or general lack of—local guidelines in regard to screening and therapy; second, delays in screening and admission; third, lack of clinical decision support; and fourth, availability of PT.[5,6] The comprehensive approach implies that engagement of stockholders, education, and training to nurses and parents are as important as the technical resources for an immediate TSB quantification, and treatment. Examples presented included educational outreach in geographically disadvantaged areas that were shown to be extremely effective in reducing the incidence of KSD, thus supporting the exporting of this strategy to other areas. To that end, we strongly support the strategy of continued collaboration and the exchange of experience and expertise for transforming this approach into a global protocol. No solution will be truly complete until affordable and reliable instrumentation for diagnosis and treatment is available to all.

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**Fig. 1 J. Donald Ostrow Yellow Retreat 2019 official picture.**

## MECHANISMS OF BILIRUBIN NEUROTOXICITY AND NEW THERAPEUTIC APPROACHES

While bilirubin has been recognized as the neurotoxic agent in KSD for decades, additional mechanisms of its neurotoxicity are still emerging. Basic research investigations into understanding how and why bilirubin causes brain region-specific cell death are ongoing and could potentially lead to novel therapies. Cell-based studies from two labs presenting at DOTYR 2019 provided convincing evidence about specific bilirubin localization and activity requirements for toxicity. These data are likely to be key in developing novel drug therapies aimed at protecting neonates with severe hyperbilirubinemia.

A clear focus on translational research also emerged from the conference: The advances in unraveling the targets of bilirubin toxicity were accompanied by preclinical (animal-based) trials aimed at reversing the damage. Preterm infants continue to be recognized as an especially sensitive population, where critical steps in brain development may become targets for bilirubin toxicity. Supplementation of targeted compounds able to counteract the specific toxic action improving or even preventing CNS lesions was presented. If confirmed, these approaches might become complementary to PT, or even offer an alternative approach to treating severe hyperbilirubinemia in areas of the world where PT is not feasible.

In addition to these basic science efforts, it was evident that the most immediate clinical impact will derive from the improvement of PT, the first and most extensively used approach to treat hyperbilirubinemia. Advanced apparatuses able to avoid the potential of oxidative stress and DNA damage, as well as allowing for breastfeeding and safeguarding the mother−baby bond, guaranteeing the effectiveness of the treatment were presented.

Notably, in several geographical areas of the world, ethnic differences in the incidence of bilirubin-based diseases point towards specific genetic determinants, still not clearly identified, as contributing to the increased annual incidence of severe neonatal hyperbilirubinemia and KSD. The cooperation between countries where the most advanced technologies are available, but KSD is rare, with the countries where KSD is still common, is crucial for understanding individual genetic susceptibility to bilirubin.

## CONCLUSION

While there were many important exchanges at the 2019 DOTYR, perhaps the clearest message that came out of the retreat was the need to reach a critical mass of data out of a relatively small number of researchers. By working together to fix shared protocols to allow for a more reliable comparison of results from different laboratories and hospitals around the world, we will be able to produce the "big data" necessary to optimize research and find efficient solutions without dispersing competences and resources. It was also very clear that different areas of the world face different challenges. Despite differences in clinical priorities worldwide, we believe that the greatest opportunity to make real, impactful changes will result from this move towards synchronization of research around the idea of creating a "critical mass" in the field of hyperbilirubinemia and bilirubin neurotoxicity. Big data, ranging from clinical to the most advanced research new knowledge, are the tools needed for understanding and managing the persisting problem of severe neonatal hyperbilirubinemia. The collaborative spirit felt at this year's retreat gives us great hope that the future will be as successful as the last 2 years.

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## AUTHOR CONTRIBUTIONS

S.G. drafted the manuscript and critically edited. S.M.R. assisted in drafting the manuscript and critically edited. Both S.G. and S.M.R. gave final approval for the version submitted for publication.

## ADDITIONAL INFORMATION

**Competing interests** The authors declare no competing interests.

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