Taking Stock of Hemophilia, Immune Thrombocytopenia, and Bone Marrow Failure

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This issue of the *Journal* continues with the second of the two-part symposium on benign hematology with expert reviews addressing hemophilia, immune thrombocytopenia (ITP), and bone marrow failure syndromes. The bleeding disorders in children, particularly hemophilia, are of considerable concern to pediatricians. India may have over 70,000 patients with hemophilia A and B [1], which is deemed to be a high-cost, low-volume disease [2], and is the most common inherited bleeding disorder encountered in tertiary care centers [3]. It is critical to identify inherited bone marrow failure syndromes (IBMFS) among the children with aplastic anemia to avoid inappropriate use of immunosuppressive treatment. The pediatrician is the point of first contact when a child develops signs of ITP, so the review of current management guidelines will serve as a vital resource for rendering an appropriate decision.

Puthenveetil et al. have reviewed state of the art in the management of hemophilia [4]. There have been numerous advances in the past decade, including long-acting factor products, non-factor products, and potentially curative interventions such as gene therapy [4]. Extended half-life rFVIII sustain higher trough factor levels for longer periods resulting in reduced bleed rates. The reduced frequency of administration enables improved compliance with prophylaxis regimens [4]. Efficizumab is a humanized bispecific monoclonal antibody that binds and bridges FX and FIXa and effectively performs the function of the missing FVIIIa in patients with hemophilia A. It was granted first Breakthrough Therapy Designation in

2015 and was approved by the Food and Drug Administration (FDA) in November 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors. It was approved by the European Commission in February 2018 for routine prophylaxis of bleeding episodes in people with hemophilia A with factor VIII inhibitors. The high cost of extended-half-life and non-factor products is prohibitive in low-middle-income countries (LMIC) [4]. In a recently reported study, titled, ‘HAEMOcare,’ inadequate access to hemophilia treatment centers and expert care, along with high bleeding rates, led to equivalent hemophilia-related orthopedic morbidity between hemophilia patients without and with inhibitors in a cohort of patients from five LMICs [5]. Indeed, low-dose prophylaxis with conventional factors as an alternative, efficient, and cost-effective strategy is encouraging and must be publicized for preventing chronic hemophilic arthropathy in LMIC [6, 7].

In their review, Fassel et al. have discussed the approach to diagnosis and treatment of bone marrow failure in children [8]. Traditionally, a chromosomal breakage test has been requested in young patients with aplastic anemia to exclude Fanconi anemia, before the administration of the immunosuppressive combination of anti-thymocyte globulin (ATG) and cyclosporine [9, 10]. Because of phenotypic variability, the diagnosis of IBMFS can be challenging. However, in recent times, the diagnosis for IBMFS has dramatically expanded with the easier availability of molecular diagnostic techniques. Using next-generation sequencing, whole-exome, or even whole-genome, analysis may yield useful information in rare syndromes on genetic etiology or a targetable polymorphism/mutation [8]. The response rates to immunosuppressive therapy in children with aplastic anemia in India are not as high as reported from the higher income countries [10, 11]. It may be partly related to a delayed administration of ATG as a consequence of late referral patterns. It is plausible, though not proven, that a missed diagnosis of IBMFS with inadvertent administration of immunosuppressive therapy, could be a contributing factor for the sub-optimal response.

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In the final review of this symposium, Singh et al. address frequently asked questions in ITP [12]. Given the common occurrence of ITP, the debate on the benefits and risks of the multitude of therapies available for ITP vs. conservative management [13–15] is familiar to all of us. Eltrombopag and romiplostim are preferred options to treat children with persistent or chronic ITP in high-income countries, but there are no guidelines on the duration of therapy [12]. It is common knowledge that the severity of clinical symptoms, instead of the platelet count, should guide decisions on the management of ITP. However, this rule is often disregarded for the presumed comfort of the family and the physician. Continuing education of parents and pediatricians to the risks and benefits of available therapeutic options is necessary to encourage the adoption of current guidelines, particularly to decide on when observation is appropriate [16]. The American Society of Hematology (ASH) 2019 guidelines for ITP make a strong recommendation for observation instead of treatment in children with new-onset ITP who have no or minor bleeding, and place a high value on avoiding splenectomy since spontaneous remission is frequent [17]. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished health-related quality of life, the ASH guidelines recommend against courses of corticosteroids longer than 7 days [17].

The reader will find the reviews on these selected topics in benign hematology - hemophilia, IBMFS, and ITP - to be timely. Familiarity with recent advances and incorporation of expert-recommended guidelines into medical practice will improve outcomes for our patients.

Compliance with Ethical Standards

Conflict of Interest None.

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