

allow for more individualized and less toxic treatments in the future.¹⁰ Third, given that a large population of patients will still require HCT for cure, novel strategies to decrease regimen related toxicity, such as the development of personalized pharmacokinetic-guided dosing algorithms, are needed.

The findings from Turcotte et al's¹ study are limited by the facts that the cohort stretches over nearly 3 decades and treatment of AML has changed substantially through the years. For example, in patients in this study who received HCT, one-third were autologous and nearly half received total body irradiation, neither of which are part of standard treatment today. Yet the long-term outcome data presented here are essential to our understanding of the late toxicity seen in AML patients and will be helpful in designing the next phase of treatment protocols. Ultimately, such protocols should optimize cure rates and long-term quality-of-life outcomes while reducing the risk of late effects.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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THROMBOSIS AND HEMOSTASIS

Comment on *Icheva et al*, page 102

Acquiring a new diagnostic approach for aVWS

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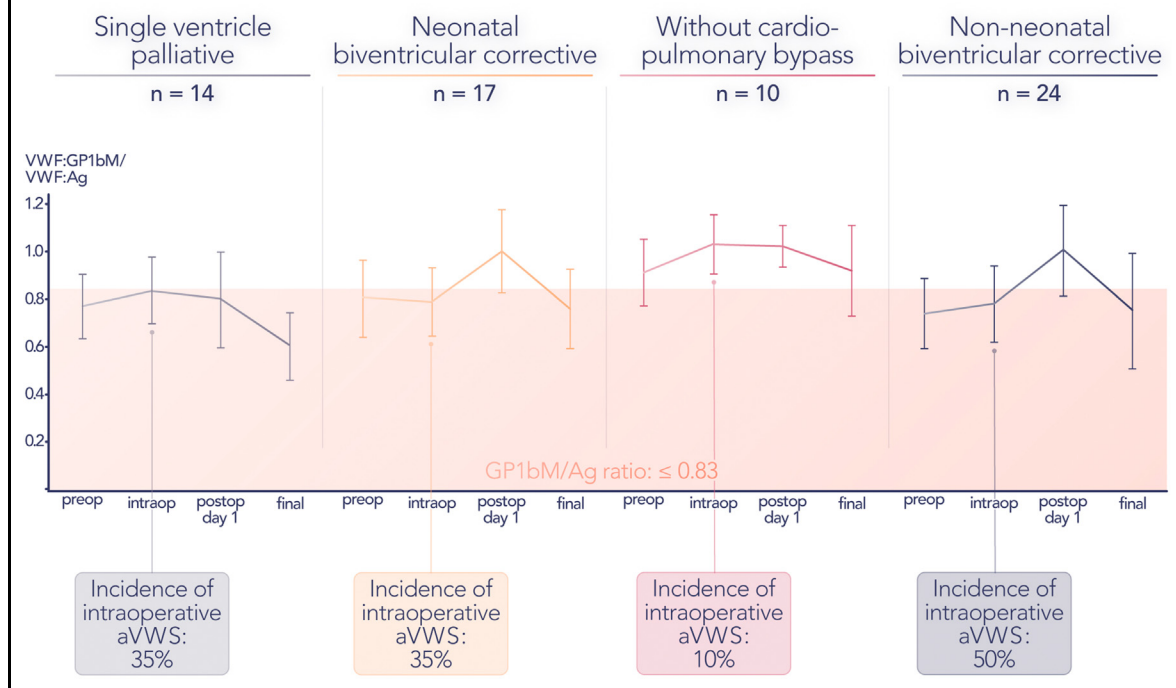
In this issue of *Blood*, Icheva et al describe a new and highly predictive approach for the laboratory diagnosis of acquired von Willebrand syndrome (aVWS) in neonates and infants undergoing surgery for congenital heart disease (CHD).¹ Although pediatric aVWS is a rare disease, it appears most commonly in the clinical setting of CHD, in which the shear stress-induced increase in von Willebrand factor (VWF) proteolysis causes the loss of high molecular weight multimers (HMWM).² Understanding possible risk factors of bleeding in infants with CHD is crucial for this patient population because neonates and small infants, in particular, are susceptible to the coagulopathic effects of cardiopulmonary bypass, almost invariably requiring the use of blood components and other procoagulant interventions.^{3,4}

Historically, a significant barrier to the timely diagnosis of aVWS has been the lack of readily available and accurate laboratory testing. Individual and pre-analytical variables affect the sensitivity of traditional laboratory testing for aVWS, particularly with ristocetin-based activity testing.⁵ The gold standard for diagnosing aVWS, the VWF multimer analysis, is time consuming and unavailable on-site at many institutions. A key advancement in recent years has been in the measurement of functional assessment of VWF, with ristocetin-based activity tests gradually being supplemented or replaced by assays based on the binding of VWF to a recombinant platelet glycoprotein (GP1bM), which show greater precision and higher sensitivity.⁶ In this prospective cohort study, Icheva et al take the next step of investigating how this new testing can be used in the identification of aVWS.

The investigators screened all patients with CHD aged 0 to 12 months requiring

corrective or palliative cardiac surgery over a 17-month time frame and achieved a high enrollment percentage (95% of eligible infants enrolled in the study). Participants underwent detailed coagulation testing at 4 standardized time points (preoperative, intraoperative, postoperative day 1, and final testing, typically within the first 2 weeks after surgery) (*figure*). VWF:GP1bM testing was performed using a commercially available test, and at the authors' institution, only 1 hour elapses from blood collection to the result. In their analysis, the authors compared the predictive value of the GP1bM/VWF:antigen (Ag) ratio, the VWF:collagen binding/VWF:Ag ratio, and peak systolic echocardiographic gradients with the gold standard HMWM ratios. Among the algorithms studied, the GP1bM/VWF:Ag ratio provided the best predictive value for identifying aVWS and correlated strongly with the HMWM ratio. Another key finding from this work was that a GP1bM/VWF:Ag cutoff value of <0.83,

VWF:GP1bM/VWF:Ag ratio in infants with CHD



GP1bM/VWF:Ag ratio over the perioperative course of infants with congenital heart disease. The intraoperative incidence of aVWS (defined as a ratio ≤ 0.83) ranged from 10% in the subgroup undergoing surgery without cardiopulmonary bypass to 50% in non-neonates undergoing biventricular corrective procedures. Professional illustration by Somersault18:24.

as opposed to the generally recommended cutoff of <0.7 , was found to be the optimal cutoff because it provided better sensitivity. To transfer these research findings to the bedside, more institutions will need to adopt a VWF:GP1bM activity assay as an on-site test. The authors also highlight that institutions should invest time and resources to develop in-house cut-off values for identifying low GP1bM/VWF:Ag ratios.

The large sample size of this study ($n = 65$ in the final analysis) compared with historical literature in this field also improves our understanding of the epidemiology of aVWS in infants with CHD. In this cohort, a substantial number (approximately one-third) of neonates and infants undergoing various surgical procedures for palliation or correction of CHD were found to have laboratory evidence of aVWS. However, only 1 patient subgroup (Group II, neonates undergoing biventricular corrective surgery) showed possible significant differences in blood loss (indirectly measured by supplemented blood

components and chest closure times) according to aVWS status. However, it is impossible to know how much of this difference (fresh frozen plasma, platelets, packed red blood cells, and fibrinogen were all given more commonly in those with aVWS) was based on correction of laboratory values as opposed to perceived blood loss. In addition, all patients receiving cardiopulmonary bypass (Groups I, II, and IV) received intraoperative tranexamic acid as standard care. Postoperative bleeding occurred in $<10\%$ of patients ($n = 6$ patients total), and the incidence of bleeding events (nor the amount of chest tube drainage over the first 24 postoperative hours) did not differ between aVWS⁺ and aVWS⁻ patients.

These findings highlight continued knowledge gaps unable to be filled by the current study. What is the clinical significance of a laboratory diagnosis of aVWS? Would routine correction with VWF concentrate in such patients provide clinical benefit or simply increase costs and thrombosis risk for this patient population? Indeed, clinical trials have not evaluated the value of

screening for and treating aVWS in previously asymptomatic patients,⁷ and experts have argued that the diagnosis should only be made in the presence of bleeding symptoms. On the other hand, these are very young patients facing a highly invasive surgery who may not have had time to manifest bleeding symptoms.^{5,7} In fact, in a cohort of older pediatric patients with aVWS (aged 5 months to 19 years), 15 of 16 (94%) had bleeding symptoms at the time of presentation, with heavy menstrual bleeding and epistaxis being most common.⁸ And unlike adults, cardiopulmonary-related aVWS remains uncorrected in most pediatric patients after surgery (as supported by the current study and initially demonstrated in the authors' initial case series).^{3,9}

This work by Icheva et al represents a significant step towards a more accurate and timely diagnosis of aVWS. This advance should lead to more routine preoperative screening for aVWS and an increasing understanding of clinical bleeding risk. It is intriguing to wonder whether standardized use of antifibrinolytics in combination with targeted replacement of VWF concentrate

could help to change the current paradigm, in which large volumes of donated blood components (an increasingly scarce global resource) are routinely given to neonates and infants undergoing repair of CHD.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on *Yakymiv et al*, page 111

CD39-CD73-adenosine effects in Sézary syndrome

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In this issue of *Blood*, Yakymiv et al¹ provide evidence that malignant CD4+ T-cells derived from patients with Sézary syndrome (SS), the leukemic variant of cutaneous T-cell lymphoma (CTCL), express high levels of the CD39 and CD73 ectonucleotidases, which may contribute to an immunosuppressive microenvironment. Treatment of advanced stages of CTCLs remains challenging, reflecting a low rate of durable remissions despite recent approval of several targeted therapies, such as brentuximab and mogamulizumab. Unlike mature nodal T-cell malignancies, CTCLs derived from skin-homing memory CD4+ T-cells have very high tumor mutational burden due to ultraviolet radiation,² but responses to checkpoint inhibition remain modest.³ This level of response reflects the difficulty of enhancing T-cell immune responses in T-cell malignancy, and so an understanding of the tumor microenvironment in CTCLs remains a critical need.

Specifically, Yakymiv et al show that SS patients with high expression of CD39 have higher plasma levels of adenosine monophosphate (AMP) in vivo, compared to those of healthy donors, and when these CD39+ tumor cells are co-cultured in vitro with human

pulmonary microvascular endothelial cells, increased concentrations of adenosine are generated. Furthermore, they report that CD3/CD28-mediated proliferation of CD8+ T-cells from SS patients and healthy donors is inhibited in the presence of adenosine triphosphate

(ATP). In contrast, when inhibitors of the adenosine receptor (A2AR) are added, ATP does not inhibit proliferation of CD8+ T-cells. Although Yakymiv and colleagues did not analyze the effects of ATP on the proliferation of CD4+ malignant T-cells, Sonigo et al showed that both anti-CD73 antibody and A2AR inhibition only partially restored proliferation of the CD4+ malignant T-cells from SS patients.⁴ These results, albeit in a small cohort of SS patients, are compelling and suggest that the CD39/CD73/adenosine axis promotes immunosuppression in SS, enhancing our understanding of the tumor microenvironment in CTCL (see figure).

CD39 and CD73 are members of a family of ectonucleotidases that are expressed in a wide range of cancers to promote a favorable tumor microenvironment.⁵ In both solid and hematologic malignancies, extracellular ATP accumulates at levels much higher than those observed in healthy tissues, owing to tumor cell death and metabolic stress.⁶ Extracellular ATP acts as a danger signal, triggering proinflammatory responses, but CD39 hydrolyzes ATP to AMP, which is sequentially converted by CD73 into immunosuppressive adenosine, allowing the tumor to evade immune monitoring. Adenosine may affect the tumor microenvironment directly or by exosome-mediated cellular exchange of CD39. Other ectonucleotidases include CD38, CD157, and CD203a, which also generate adenosine via the sequential catabolism of NAD⁺. Although high expression of CD39 was initially characterized as a distinguishing feature of Treg cells, mediating their immunosuppressive abilities,⁷ many immune effector cells express CD39, including memory CD4+ T-cells with an exhausted phenotype that is recognized as a feature of SS cells. The bioavailability of adenosine is regulated by adenosine deaminase, and the docking station for adenosine deaminase is CD26, which intriguingly is consistently lost on malignant CD4+ T-cells in SS.

Functional studies have established a role for the CD39/CD73/adenosine pathway in other hematologic malignancies, notably chronic lymphocytic leukemia, which includes a plethora of effects on regulation of cellular components of the immune system to ensure maintenance of