Given the high mortality rate of sepsis and increasing antimicrobial resistance, there is a great need for new therapeutic options for sepsis. The work of Carestia et al could have clinical implications. Future studies may determine whether the efficacy and safety of ASA the authors describe here in models of sepsis induced by IV or intraperitoneal injection of *S aureus* also apply to other models and with different bacterial species. Platelets have indeed been shown to continuously prevent bleeding in various inflammatory situations, where they intervene to both inhibit bacterial growth and prevent bleeding at the primary site of infection.[10]

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TRANSPLANTATION

Comment on Schultz et al, page 1287

A few steps on the long road toward biomarkers in GVHD

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In this issue of *Blood*, Schultz et al report the biomarker profiles of 241 patients 3 months after allogeneic hematopoietic stem cell transplantation (alloHSCT) who were followed for the development of chronic graft-versus-host disease (cGVHD) or late acute GVHD. The patients were part of the prospective ABLE (Applied Biomarker of Late Effects of Childhood Cancer) trial, which was the first prospective multicenter biomarker trial stringently applying the National Institutes of Health (NIH) criteria for diagnosis of cGVHD in pediatric and adolescent patients.[1]

The authors report multiple provocative findings. First, the biomarker profiles of patients who later developed signs of immune-mediated damage with distinctive but not diagnostic features of cGVHD by NIH criteria and required immunosuppressive treatment did not differ significantly from those of patients with NIH-defined cGVHD. This suggests that cGVHD may involve more targets than currently included in the NIH consensus criteria, which classify cGVHD based on the most frequently involved organs.[2] Fifteen percent of the patients in the analyzed cohort showed immune-mediated damage that did not fulfill the NIH definition, likely similar to what has been labeled by a European Society for Blood and Marrow Transplantation/NIH/Center for International Blood and Marrow Transplant Research taskforce as "undefined other cGvHD."[3(pp1401-1415)] Patients with signs of immune-mediated damage lacking NIH-defined manifestations may eventually be classified as having cGVHD in future trials or at least be included in further analysis of biomarkers, assuming the finding can be confirmed in other study cohorts.

Second, although the NIH consensus criteria provide clinical definitions for the distinction of late acute GVHD from classic cGVHD,[2] the data provide hints of a biological distinction, where patients with both entities have B-cell abnormalities, but the expansion of naïve $CD4^+$ T cells seems to be restricted to patients developing cGVHD. Interestingly, metalloproteinase 3 (MMP3), ST2, and soluble CD13 (sCD13) were confirmed as prognostic biomarkers of cGVHD, whereas the previously proposed plasma biomarkers CXCL9 and osteopondin were not significant in either entity for unknown reasons.[4] The frequent identification of MMP3 suggests that remodeling is a distinctive feature of cGVHD. Heterogeneity in biomarkers was observed in a multicenter analysis that included adult patients, with significant differences found between different cohorts.[5] This indicates the need for large verification and qualification cohorts.[6]

Third, the analysis indicates in a small subset of 14 patients that the day-100 biomarker profile (plasma biomarkers MMP3, sCD13, and ST2 and alterations of B-cell subpopulations) is not affected by the presence of active GVHD. Previous studies of sBAFF showed a significant impact of corticosteroids.[7] If this is confirmed in larger studies, trials evaluating biomarkers at day 100 after alloHSCT may include patients with active GVHD, which will help with accrual and better represent a high-risk group.

Fourth, age has an impact on biomarkers, indicating the need for age-specific pediatric cohorts in the identification of biomarkers for acute GVHD and cGVHD. For example, children age <12 years rarely develop de novo onset of cGVHD.[8]

Finally, the analysis reveals indirectly a continuing pathophysiology from acute

to cGVHD, because the abnormalities in immunoregeneration were most prominent in cGVHD. Patients with acute GVHD seemed to have profiles located between those of patients with tolerant and cGVHD when examined by a machine-learning approach.

In summary, the analysis provides important insights into the utility of biomarkers in predicting the course of patients 3 months after transplantation. Despite a relative high number of recruited patients, different subgroups remain too small to permit valid conclusions. The results will require additional replication cohorts followed by qualification before application in clinical care.[9] This obstacle is unlikely to be resolved by pure quantity, given the complexity of the disease, different organ patterns, and varying disease courses. Future trials should incorporate transplantation baseline parameters such as stem cell and donor source, age, conditioning regimen, GVHD prophylaxis, GVHD course, and organ pattern together with the analyzed biomarkers, potentially including changes over time to account for time and treatment effects and applying machine-learning techniques as already piloted.[10]

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