healthy relatives who did not have complement mutations or antifactor H antibodies. Another important control group in this study was 15 patients with C3 glomerulonephritis or immune complex membranoproliferative glomerulonephritis who developed kidney disorders due to fluid-phase complement activation. In the reported results, the authors found that serum of patients with either acute aHUS or aHUS in remission deposited more C5b-9 on ADP-activated HMEC-1 than serum of control subjects (see figure). It is worth mentioning that 38% of aHUS patients in this study (14 out of 36) did not have any detectable complement mutations or antifactor H antibodies. Only serum of patients with acute aHUS deposited more C5b-9 on resting HMEC-1 than control sera. Interestingly, serum of healthy mutation carriers, and not serum of healthy noncarriers, deposited more C3 and C5b-9 on ADP-activated HMEC-1 compared with control sera. The amount of C5b-9 deposited on ADP-activated HMEC-1 by almost all of the serum samples from patients with glomerulonephritis due to fluid-phase complement activation (14 out of 15) was similar to that by control sera. From these results, one might conclude that an increase in C5b-9 deposition on ADP-activated HMEC-1 can be helpful in the diagnosis of aHUS (acute phase or in remission).

The authors found that treatment with eculizumab resulted in normalization of serum-induced C5b-9 deposition on ADP-activated HMEC-1 in patients with aHUS. Interestingly, the dosage of eculizumab was titrated according to the results of this assay in 4 patients. Normalization of the serum-induced C5b-9 deposition with higher doses of eculizumab coincided with improvement in the clinical parameters in 2 patients, and conversely, reducing the dosage or increasing the interval between infusions of eculizumab in 2 patients based on the results of this assay was not associated with any worsening of their clinical outcome.

In summary, the in vitro functional complement assay based on the serum-induced C5b-9 deposition on endothelial cells is potentially useful in the diagnosis of aHUS and in monitoring its treatment. The problems with this assay are that it is technically complex and cumbersome, hindering its widespread clinical use in its current form, and it cannot detect complement dysregulation due to the deficiency of cell-surface complement regulators (thrombomodulin and MCP) and aHUS due to mutations in cytoplasmic diacylglycerol kinase c.6

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Clinical Trials & Observations
Comment on Collins et al, page 1727

Rotem in postpartum hemorrhage

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In this issue of Blood, Collins et al describe the value of fibrinogen and fibrinogen-based Rotem (Fibtem) as a predictors of severe postpartum hemorrhage among women with persistent postpartum hemorrhage.1 Fibtem seems to be a promising, fast, point-of-care measure for progression to severe hemorrhage. However, before implementation in clinical practice, there are a number of questions that need to be addressed.

Persistent postpartum hemorrhage is frequently complicated by coagulopathy even before the development of dilutional coagulopathy. If unnoticed, coagulopathy may contribute to massive unstoppable hemorrhage and ultimately death. Early assessment of coagulation status has been recommended to identify, and subsequently correct, coagulation abnormalities.2 Unfortunately, the turnaround times for the recommended standard tests (platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen concentration) are generally longer than 60 minutes, implying that by the time the results are available, the coagulation status may have changed considerably. Thus, rapidly available results of point-of-care tests, such as Fibtem, could significantly improve the outcome of women with postpartum hemorrhage.

The findings of Collins et al show that Fibtem A5 measured after 1000 to 1500 mL postpartum hemorrhage was available 10 minutes after venipuncture and associated in a dose-response manner with progression to more severe hemorrhage.3 Given the perceived need for a faster test to diagnose coagulopathy in women with persistent postpartum hemorrhage, it is tempting to think that Fibtem should immediately be included in the series of tests for the assessment of coagulation status. However, there are several arguments against this notion.

Fibtem results could improve clinical outcomes of women with persistent postpartum hemorrhage in 2 ways: first as a predictor of severe postpartum hemorrhage, and second as a diagnostic for coagulopathy. With respect to its role as a predictor, the Fibtem test is still in a preclinical phase. The successive phases of prognosis research are identification of the predictor, followed by development of a prediction model, external validation of the model, and finally assessment of the clinical impact of the model.4 Fibtem is now for the first time identified as predictor of severe postpartum hemorrhage5 and is therefore still in an early preclinical phase. The
appropriate next step is the development of a multivariate prognostic model that combines relevant prognostic indicators, including primary cause of postpartum hemorrhage and other clinical characteristics. After validation, this model could serve to categorize women according to a low or a high risk for severe postpartum hemorrhage in order to be able to adjust treatment strategies accordingly.

A second potential role for Fibtem in clinical practice would be to improve the timely diagnosis of coagulopathy. However, the clinical actions that follow the diagnosis of coagulopathy as assessed with Fibtem (possibly combined with other tests) have not been established. The results of the ongoing randomized trial studying whether fibrinogen concentrate can improve the outcome of women with moderate postpartum hemorrhage and low Fibtem values (ISRCTN46295339) will need to be awaited. Yet, even if fibrinogen concentrate is proven to be efficacious in women with low Fibtem values, we still don’t know whether the Fibtem with-or-without-fibrinogen-concentrate strategy is better (optimal cost-effectiveness) than other strategies.

Besides the strategy of Fibtem measurement possibly followed by fibrinogen concentrate infusion, there is a myriad of other strategies to treat persistent postpartum hemorrhage. The strategies can be roughly categorized as laboratory driven and formula driven. In the laboratory-driven strategies, treatment decisions depend on laboratory parameters and treatment triggers to guide treatment decisions during persistent postpartum hemorrhage. The formula-driven strategies use a prearranged delivery system of (blood) products in various mixtures of products, such as tranexamic acid, red cells, plasma, platelets, and coagulation factors, to stabilize a hemorrhagic patient. These strategies have not been defined for postpartum hemorrhage, but it would be worthwhile to consider development of such a strategy. Coagulopathy and reduction in clotting factors can develop rapidly and soon after having a reassuring test result. With the formula-driven strategy, all women presenting with persistent postpartum hemorrhage can be treated without delay in a standardized way. The disadvantage of such a formula-driven strategy is that this strategy is not individualized and may therefore lead to both over- and undertreatment. The next sensible step would be to compare a well-designed, evidence-based, formula-driven strategy with a well-designed, evidence-based, point-of-care-test-driven strategy. The findings of Collins et al provide evidence in favor of Fibtem as a test in the laboratory-driven strategy.

Particularly noteworthy in the report by Collins et al is the observation that in the multivariate model, fibrinogen is no longer associated with progression to severe postpartum hemorrhage, whereas Fibtem remains appreciably associated. This suggests that in these early phases of postpartum hemorrhage, other coagulation factors involved in clot formation, not fibrinogen concentration, might be more important for progression to severe postpartum hemorrhage. So an important question is, is fibrinogen at low normal concentrations causally related to progression to severe hemorrhage, or is it but an indicator of the severity and stage of the postpartum hemorrhage?

An additional point that needs to be addressed is laboratory quality control. The TEG-Rotem working group reported large differences in test results among laboratories.8 Fibtem is a relatively costly commercial test, widely implemented in the thoracic surgery setting, and commercial forces are increasingly pushing its application in labor wards. Despite the promising results of Collins et al presented in this issue of Blood, we should bear in mind that new tests first need to undergo scrutinized testing for their clinical usefulness. Otherwise, implementation of this test might lead to needlessly high increases in health-care costs with insufficient gain or even loss in patient outcomes.

Postpartum hemorrhage is common and potentially lethal. The study described by Collins et al provides promising findings with regards to the prediction of severe postpartum hemorrhage and early diagnosis of coagulopathy. A number of issues have to be addressed before implementation of Fibtem in the treatment strategy for women with ongoing postpartum hemorrhage. Thus, clinicians interested in Fibtem are encouraged to use the test in the framework of a well-designed scientific study.

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Comment on Newson et al, page 1748

Cellular dynamics of resolving inflammation

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In this issue of Blood, Newson et al determine the dynamics of inflammatory cell recruitment and their diversification into functionally distinct, cellular subsets in a previously uncharacterized “postresolution” phase of inflammation. The postresolution tissue retains some of the recruited populations of monocytic and lymphoid cells and remains in a state of “adaptive homeostasis” long after inflammation has resolved.
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