Laboratory Evaluation

In a majority of newborns with a hemorrhagic disorder, history and physical examination alone will point to the correct diagnosis, with laboratory tests providing confirmation. The initial workup usually includes a PT, APTT, TCT, fibrinogen level, platelet count, and on rare occasion, a bleeding time or PFA-100 assay. Abnormalities in these tests will usually guide the selection of additional tests such as specific factor assays (Fig. 76–3). Deficiencies of FXIII, α_2AP, and PAI do not alter the results of the screening tests, and these must be measured directly if deficiencies are suspected.

Ideally, samples should be taken from a peripheral vein. This approach often is not feasible in small preterm infants or in infants with difficult venous access after repeated sampling. If samples are drawn from central lines, even minute contamination with heparin may give erroneous results. In these instances, preanalysis incubation of the sample with protamine or heparinase may be used to eliminate heparin contamination (Ellis, 1993; Keller et al, 1998).

All laboratory results must be considered in the context of age-related reference values. Differentiation of hereditary and acquired deficiencies from physiologic values can be difficult for most coagulation proteins, a problem unique to newborns.

Management

The appropriate management of an infant with a hemorrhagic disorder is dependent on the current identification of the hemostatic defect. Options for replacement therapy include specific factor concentrates, fresh frozen plasma (FFP), platelet concentrates, and cryoprecipitate. Other therapeutic considerations are related to whether venous access can be maintained, particularly if an exchange

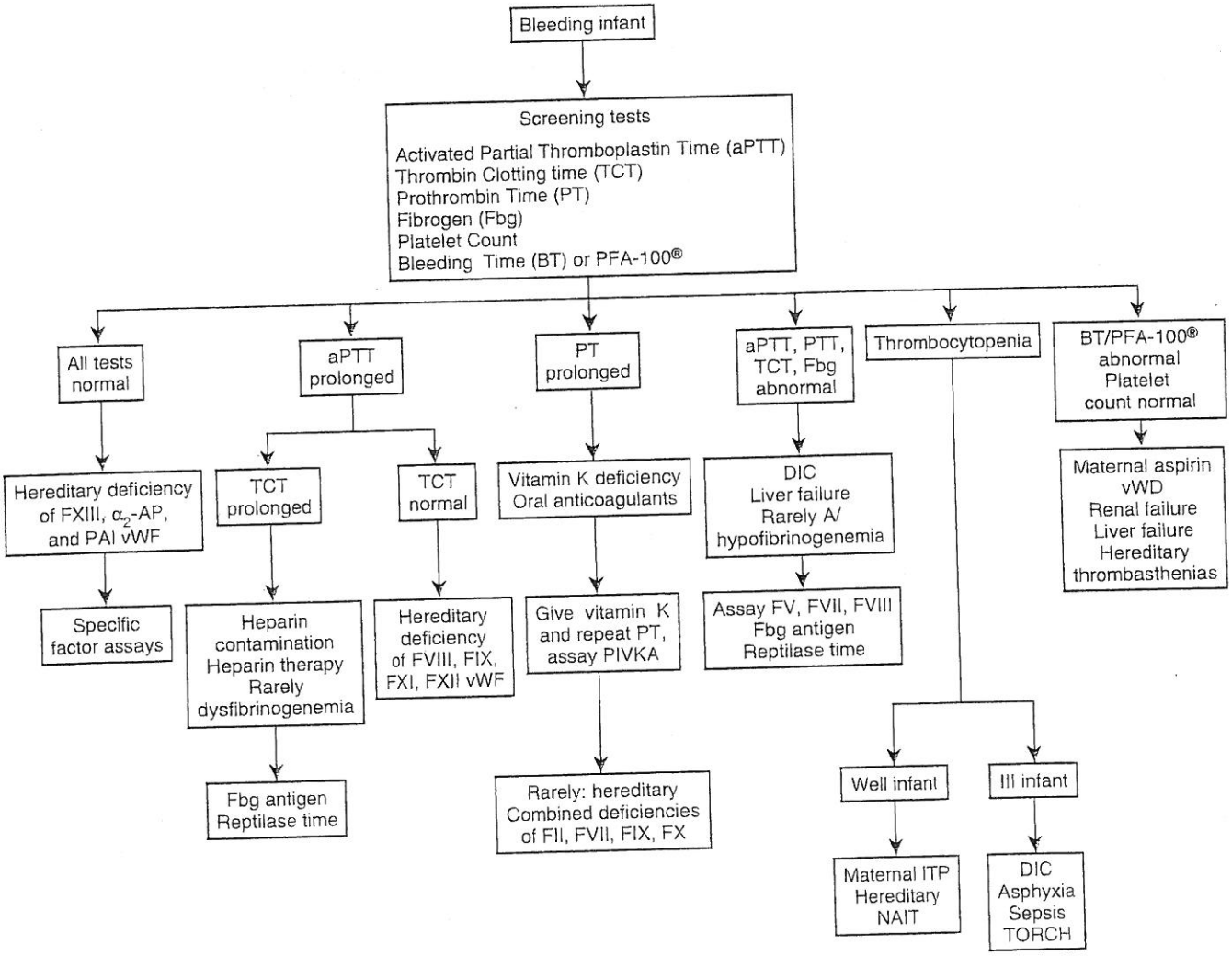

FIGURE 76–3. Flow diagram for the evaluation of a bleeding newborn. α_2AP, α_2-antiplasmin; APTT, activated partial thromboplastin time; BT, bleeding time; DIC, disseminated intravascular coagulation; F, factor; Fbg, fibrinogen; FSPs, fibrin split products; ITP, idiopathic thrombocytopenic purpura; NAIT, neonatal alloimmune thrombocytopenia; PAI, plasminogen activator inhibitor; PIVKA, protein induced in the absence of vitamin K; PT, prothrombin time; TCT, thrombin clotting time; TORCH, *t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus infection, *h*erpes simplex; vWD, von Willebrand disease; vWF, von Willebrand factor. *(Data from Kisker, 1998.)*

A number of variables have been shown to affect the results obtained with the PFA-100 and these include:

Variable	Effect
Citrate concentration	Laboratories must use a fixed citrate concentration
Collection time	How the sample was collected and transported to the lab. The tests must be performed within 4 hours of collection
Haematocrit	Closure times increase progressively with decreases in haematocrit. Conversely, CTs are shortened in the neonate due to their higher haematocrit.
Platelet count	Closure times increase progressively as the platelet counts falls below 100 x 10^9/L
Blood Group and VWF levels	Closure times correlate inversely with plasma VWF activity levels and may be increased in blood group O patients for the same reason [Blood group O individuals have lower VWF levels.]
Drugs:	COX inhibitors such as aspirin and NSAIDs usually prolong the closure time of the CEPI cartridge but not the CADP cartridge. The effects of ADP receptor blockers such as Clopidogrel is unpredictable. Inhibition of the GpIIb/IIIa receptor is associated with a significant prolongation of both cartridges.
Acquired platelet function defects	Cardio-pulmonary bypass Liver disease Uraemia
Some foods	Generation of false positives particularly with the CEPI cartridge. This is due probably to ingested foods or drugs. An abnormal PFA-100 result is not, therefore, diagnostic.

Aspirin Resistance: The PFA-100 is often used to establish the presence of absence of aspirin resistance. The frequency of aspirin resistance is unknown, but estimates range from 5-60%. The mechanism of aspirin resistance is unknown but proposed mechanisms include poor patient compliance, poor aspirin absorption, increased platelet

hypersensitivity to agonists, increased COX activity, and polymorphisms in the Gp IIIa receptor and the COX enzyme. Aspirin resistance appears to be dose related in some patients and may be overcome with higher doses.

Interpretation

The following table summarises some of the abnormalities that have been reported with the PFA-100.

Disorder	CT Collagen-ADP	CT Collagen-EPI
Normal	N	N
Aspirin and NSAIDs	N	↑
ADP receptor disorders including the use of Clopidogrel	N or ↑	N or ↑
BSS	↑	↑
GTT	↑	↑
VWD	↑	↑
Platelet-Type VWD	↑	↑
Dense Granule Deficiency	N or ↑	N or ↑
Primary Secretion Defects	N or ↑	N or ↑
Gray Platelet Syndrome	↑	↑
MYH9-related Disorders	N	↑
Scott Syndrome	N	N
MDS	N or ↑	N or ↑
Liver Disease	↑ [possibly as a result of ↓ Hb]	↑ [possibly as a result of ↓ Hb]
Uraemia	↑ [possibly as a result of ↓ Hb]	↑ [possibly as a result of ↓ Hb]

Reference Ranges

Reported reference ranges for closure times are:

- 78 - 199 seconds for the CEPI cartridge
- 55 - 137 seconds for the CADP cartridge