Coagulation Abnormalities in Cystic Fibrosis

Diane M. Komp, M.D.** and Robert F. Selden, Jr., M.D.***

Coagulation status of patients with cystic fibrosis was investigated because of the major problems of hemoptysis and gastrointestinal hemorrhage. Although gastrointestinal bleeding was frequently associated with hypoprothrombinemia, gastrointestinal ulceration and hemoptysis due to bronchiectasis were more common than bleeding due to a coagulation defect. Only patients with advanced pulmonary disease who had hepatosplenomegaly or abnormal liver function tests were subject to hypoprothrombinemia. Mild thrombocytopenia, probably due to hypersplenism, was present in several patients. In relatively few patients coagulation was impaired enough to cause bleeding. During times of stress, three patients with liver disease were shown to have increased plasma fibrinolytic activity. Although it was not the cause of clinical bleeding in these patients, it should be considered as a possibility in bleeding patients.

Bleeding difficulties such as hemoptysis and hema-
temesis are not uncommon in patients with cystic fibrosis and at times are life-threatening. Impaired liver function, malabsorption and cor pulmonale are complications of the disease that may contribute to coagulation abnormalities. In a prospective study of 59 patients with cystic fibrosis, coagulation tests were performed on 85 samples obtained.

MATERIALS AND METHODS

Pulmonary status was assessed by a modification of the Shwachman system. Patients thus evaluated were then classified as having either “good” or “poor” pulmonary status.

Liver function tests performed included total and direct bilirubin, total protein, albumin and globulin concentrations, alkaline phosphatase and serum glutamic pyruvic transami-
nase.

Coagulation studies performed included prothrombin, partial thromboplastin, serial thrombin and euglobulin lysis times, assays for factors II, V, VII-X complex and VIII, fibrinogen level and platelet count according to modifications of standard methods. Fibrinogen degradation products (FDP) were detected qualitatively by double gel diffusion of thrombin-treated sera utilizing rabbit antihuman fibrinogen antiserum. Screening tests were also performed for cryoplasminogen and fibrin stabilizing factor (FSF).

RESULTS

Prominent abnormalities noted included thrombocytopenia, prolonged prothrombin and partial thromboplastin times associated with decreased lev-

els of factor II and the VII-X complex. Since prolongations of partial thromboplastin times were related to deficiencies of the prothrombin complex, discussion will be limited to the prothrombin time. Factors V and VIII and fibrinogen were normal.

Variables noted to correlate highly with abnormalities of the prothrombin complex were pulmonary status and systemic antibiotic administration (Table 1). When patients were divided into groups according to pulmonary status, those with good pulmonary status were not subject to prothrombin deficiency despite the presence of organomegaly, abnormal liver function tests or systemic antibiotic administration (Table 2). However, patients with poor pulmonary status were much more at risk to prothrombin deficiency if organomegaly or abnormal liver function tests were present (Table 3). Since all patients in the latter group received antibiotics, no judgment as to their role can be made.

*Presented at the Tenth Annual Meeting, Cystic Fibrosis Club, Atlantic City, April 29, 1969. Supported in part by USPHS Hematology Training Grant No. T01-AM 05258.
**Assistant Professor of Pediatrics, University of Virginia School of Medicine, Charlottesville.
***Hyland Laboratories, Los Angeles, California.
Comparison of groups showed different trends for thrombocytopenia. Significant differences were not demonstrated when compared for pulmonary status or antibiotic administration (Table 1). Patients with good pulmonary status showed significantly lower platelet counts in the presence of organomegaly (Table 2). In this same group of patients, the platelet count was not influenced by antibiotic administration or liver function abnormalities. The same trend was seen in patients with poor pulmonary status.

Regardless of pulmonary status or antibiotic administration, patients without organomegaly tended to have higher platelet counts than the mean for normal children of the same age range.

Three children studied during hospitalization had evidence of increased fibrinolytic activity evidenced by short euglobulin lysis times, prolonged serial thrombin times and fibrinogen degradation products in their sera. None of these patients had depression of fibrinogen, factors V and VIII or platelets. All had advanced liver involvement. Two had clinical bleeding that stopped with administration of parenteral vitamin K. Vitamin K had no influence on euglobulin lysis time, serial thrombin time and fibrinogen degradation products, but did correct the prothrombin and partial thromboplastin times. These three patients also had absence of FSF at the time of fibrinolytic activity. Subsequent studies of these three patients as outpatients showed no evidence of increased fibrinolytic activity in spite of continuing poor liver function.

No coagulation abnormalities were found in patients with hemoptysis (five) or epistaxis (one). Gastrointestinal bleeding was associated with hypoprothrombinemia in two and radiologic evidence of ulceration in one.

### Discussion

In patients with good pulmonary status, the administration of broad-spectrum antibiotics with subsequent alteration of the gut flora does not appear to reduce the amount of vitamin K available for absorption enough to reduce the synthesis of the prothrombin complex even in the face of abnormal liver function tests or organomegaly. The patients reported by Torstenson et al. with vitamin K malabsorption had not received pancreatic enzyme therapy and represent a different population than our patients, all of whom had adequate control of steatorrhea prior to the time of study.

Patients with poor pulmonary status did show alteration in prothrombin synthesis which was influenced by liver function. Even in this group, only four patients had prolongation of prothrombin times sufficient to cause bleeding. All but one patient to whom parenteral vitamin K was given responded. Subsequent dietary supplementation of water soluble vitamin K has been adequate in several to keep prothrombin times close to normal. Whether oral supplementation will give a false sense of security in larger numbers of patients remains to be determined. Although no comparisons could be made to patients with poor pulmonary status not receiving antibiotics, it is reasonable to expect that reduction of vitamin K may occur to a significant extent by alteration of the gut flora in patients with more advanced liver disease. Our data indicate that relatively few patients with cystic fibrosis require supplemental vitamin K.

Thrombocytopenia of a mild degree was present in patients with organomegaly. The lack of correlation with liver function tests, pulmonary status and antibiotic administration would tend to incriminate hypersplenism as the etiology. None of these pa-

---

### Table 1—Mean Prothrombin Times and Platelet Counts for All Patients Studied

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Prothrombin Time (sec)</th>
<th>Platelet Count (per mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good pulmonary status</td>
<td>11.8</td>
<td>320,000</td>
</tr>
<tr>
<td>Poor pulmonary status</td>
<td>14.2</td>
<td>208,000</td>
</tr>
<tr>
<td>Receiving antibiotics</td>
<td>12.9</td>
<td>324,000</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>11.6</td>
<td>322,000</td>
</tr>
<tr>
<td>Normal range</td>
<td>10.5-13.5</td>
<td>200-400,000</td>
</tr>
</tbody>
</table>

### Table 2—Mean Prothrombin Times and Platelet Counts in Patients with Good Pulmonary Status

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Prothrombin Time (sec)</th>
<th>Platelet Count (per mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving antibiotics</td>
<td>11.9</td>
<td>300,000</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>11.6</td>
<td>335,000</td>
</tr>
<tr>
<td>Normal liver function</td>
<td>11.8</td>
<td>324,000</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>12.6</td>
<td>292,000</td>
</tr>
</tbody>
</table>

### Table 3—Mean Prothrombin Times and Platelet Counts in Patients with Poor Pulmonary Status

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Prothrombin Time (sec)</th>
<th>Platelet Count (per mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organomegaly</td>
<td>12.3</td>
<td>397,000</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>15.2</td>
<td>208,000</td>
</tr>
<tr>
<td>Normal liver function</td>
<td>&lt;0.025</td>
<td>&lt;0.0025</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>12.6</td>
<td>348,000</td>
</tr>
<tr>
<td>Significance level</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

---

CHEST, VOL. 58, NO. 5, NOVEMBER 1970
COAGULATION ABNORMALITIES IN CYSTIC FIBROSIS

patients, however, was anemic or leukopenic. In none was the platelet count reduced enough to cause bleeding. Intravascular coagulation such as is seen in some patients with cor pulmonale13-14 was ruled out by normal levels of fibrinogen, factors V and VIII and the absence of cryofibrinogen and FDP.

Increased plasma fibrinolytic activity was demonstrated in three patients but did not appear to cause bleeding. It is of interest that all three episodes were associated with stress which has been shown to increase fibrinolysis.15 In spite of continued impaired liver function, increased fibrinolysis was not present at times that these patients were stable. It is possible, however, that this may contribute clinically in some patients and should be considered as a possible cause of bleeding unresponsive to vitamin K.

Reduction of FSF in patients with increased fibrinolytic activity has been previously reported,11 presumably due to the destruction of FSF by fibrinolytic enzymes. In our studies, epsilon-amino-caproic acid was added to plasma before clot formation and the clots thus formed that were FSF deficient dissolved within two hours of the addition of 5 M urea. This would indicate that clot dissolution was not due to fibrinolysis.

Normal euglobulin lysis times in most of the patients studied and short lysis times in several would indicate that although inhibitors of plasminogen activation may be present in the lung as demonstrated by Lieberman,16 they are not usually present to excess in the plasma of patients with cystic fibrosis.

REFERENCES

1 Shwachman H, Kuleczeck LL: Long-term study of 105 patients with cystic fibrosis of the pancreas studied over a five to fourteen year period. Amer J Dis Child 96:6, 1958


8 Ratnoff OD, Menzie C: A new method for the determination of plasma. J Lab Clin Med 37:316, 1951


Reprint requests: Dr. Komp, University of Virginia Hospital, Charlottesville