The Early Diagnosis of Gram Negative Septicemia in the Pediatric Surgical Patient

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Ninety-three postoperative patients 1 day to 13 years of age had blood cultures, limulus lysate assay, determination of fibrin degradation products, white blood cell and platelet counts. Seven groups were studied. The limulus lysate assay was often positive (64%) in the presence of gram negative septicemia but there were false positives and negatives. The tests for fibrin degradation products were inconsistent. The white blood cell count was low in babies with gram negative septicemia. One hundred per cent of the infants with gram negative septicemia had a platelet count below 150,000; 71% below 100,000 (average 67,000 septic babies, 257,000 non-septic babies). The drop in platelet count with gram negative septicemia was abrupt—as much as 222,000 in 24 hours. Platelets increased when therapy was effective. Two children with gram negative septicemia had platelet counts of 50,000 and 20,000. The platelet count for patients with gram positive septicemia was 299,000, and above 150,000 in all children with ruptured and non-ruptured appendicitis and major surgery without gram negative septicemia. It was concluded that serial measurements of platelet count in the postoperative infant and child was a rapid and reliable method for early detection of gram negative septicemia and changes in platelet count in response to treatment was an indicator of the effectiveness of therapy.

GRAM NEGATIVE SEPTICEMIA is a frequently fatal complication threatening the newborn and infant surgical patient. There are multiple factors contributing to the apparent increased frequency of septicemia. With the advances in perinatal medicine, the availability of highly trained personnel, and regional newborn centers, many small premature infants suffering from severe problems are surviving. This has resulted in a population of high-risk and debilitated patients with reduced humoral and cellular defenses to infection. The common use of intravascular catheters for monitoring and endotracheal tubes and ventilators for the therapy of respiratory distress has increased the infant's exposure to bacteria.

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Large regional neonatal centers congregate many infants suffering from a variety of septic and non-septic conditions into one large unit. This allows multiple opportunities for cross contamination. With sophisticated medical technology came increased physical contact between the baby and medical personnel. Physicians of many disciplines, laboratory technicians, teams of nurses, X-ray technicians, geneticists, computer analysts, electronic technicians, and social workers flow in and out of newborn special care units. The widespread use of total intravenous nutrition introduced a long-term intravascular foreign body and infusions of concentrated sugar solutions, a combination that intensifies the danger of bloodstream infection. The common practice of administering multiple antibiotics to high-risk patients has led to the emergence of resistant bacterial strains in many centers.

Three years ago, following the development of our regional newborn center, we became alarmed by the serious threat that gram negative septicemia posed to our postoperative newborn and infant patients. As a result, we began a prospective study to: 1) determine a simple, rapid method for early detection of gram negative septicemia; 2) develop a technique that would monitor the effectiveness of therapy and 3) attempt, through a study of pediatric surgical patients, to gain insight into the pathophysiology of gram negative septicemia.

Material and Methods

Ninety-three infants and children, varying in age from one day to 13 years, were studied over a three-year

period. We chose to evaluate 5 laboratory tests: the limulus lysate assay, staphylococcal clumping and protamine sulfate tests, white blood cell count and platelet count. The limulus lysate assay[12] was used to detect circulating endotoxin. Fibrin degradation products were measured by the staphylococcal clumping*[10] and the protamine sulfate tests.[9] White blood cell count and platelet count were measured using an electronic counter.[3] In 11 babies who developed gram negative septicemia, daily platelet counts were done from admission to discharge. Blood cultures were drawn on all patients by sterile venipuncture. The blood was added to a media of liquid brain/heart infusion. The cultures were incubated aerobically at 37 C and examined twice daily. All cultures were subcultured at 24 hours, 96 hours and 10 days.

Seven groups of patients were studied.

Group 1 was comprised of babies with gram negative septicemia. (Table 1) There were fourteen patients. All had major surgery and positive blood cultures for gram negative organisms.

Group 2 was comprised of babies with no evidence of septicemia or infection. There were 22 infants who had major surgical problems similar to Group 1 and negative blood cultures during the time of the study. None of the patients had clinical evidence of infection.

Group 3 was comprised of children with gram negative septicemia. There were only two patients, postoperative major surgical operations, with positive blood cultures for gram negative organisms.

Group 4 was comprised of children with no evidence of septicemia or infection. These 20 children had major trauma or surgical procedures and were studied within 24 hours of their injury or operation. All had negative blood cultures and no infectious processes.

Group 5 was comprised of children with ruptured appendicitis. Fourteen children were studied within 12 hours of operation. Ruptured appendicitis was confirmed at operation. All patients had negative blood cultures.

Group 6 was comprised of children with non-ruptured appendicitis. Five children were studied within 6 hours of operation for acute appendicitis. All blood cultures were negative.

Group 7 was comprised of infants and children with gram positive septicemia. These 5 babies and children had major operations and positive blood cultures for gram positive organisms.

The infants and children with major operations, but negative blood cultures and no evidence of infection served as non-septic controls. The children with ruptured and non-ruptured appendicitis without a positive blood culture were studied to determine the effect upon the 5 tests of inflammatory and infectious processes without septicemia. The data from patients with gram positive septicemia were analyzed to determine the effects of gram negative in contrast to gram positive septicemia.

TABLE 1. *Diagnosis*

Group I		Group II	
Babies with gram Negative septicemia		Babies without infection	
Necrotizing Enterocolitis	7	Necrotizing Enterocolitis	2
Gastroschisis	3	Gastroschisis	5
Bowel Obstruction	1	Bowel Obstruction	2
Pyloric Obstruction	1	Pyloric Stenosis	1
Wilms' Tumor	1	Wilms' Tumor	1
Gangrene of Leg	1	Malrotation	1
		Tracheoesophageal Fistula	1
		Liver Resection	1
		Perforated Ulcer	1
		Imperforate Anus	1
		Neuroblastoma	1
		Incarcerated Hernia	1
		Diaphragmatic Hernia	1
		Polycystic Kidney	1
		Omphalocoele	1
		Meconium Aspiration	1
Total	14		22

Results (TABLE 2)

Groups 1 and 2: Infants with and without gram negative septicemia

General data. The average age of the babies with septicemia was 61 days and 7 of these infants were under one month of age. The non-infected babies had an average age of 62 days; 15 of these were under a month of age. Ten of the babies with septicemia and 12 of the non-infected babies were boys. There were predominantly three organisms grown from the bloodstream, Escherechia species, Klebsiella and *Pseudomonas aeruginosa.*

Limulus Lysate Assay. Nine of the babies with positive blood culture for gram negative bacteria (64%) had a positive limulus lysate assay. Four of the babies without a positive blood culture (19%) had a positive assay.

Fibrin Degradation Products. Fifty per cent of the infants with gram negative septicemia and 19% of the non-septic infants, had a positive staphylococcal clumping test. Fifty per cent of the babies with infection, 27% of the nonseptic babies had a positive protamine sulfate test. However, 11 of 14, or 79%, of all babies with gram negative septicemia had at least one positive test for fibrin degradation products. On the other hand, 7 of 22, or 32%, of all babies with negative blood cultures, but major operations, had at least one test positive for fibrin degradation products.

*Staphylococcal clumping test, Sigma Chemical Company, St. Louis, Missouri 63178.

TABLE 2. *Results*

	Infant		Child		Appendicitis		
	Gram Negative Septicemia	Non-Septic	Gram Negative Septicemia	Non-Septic	Ruptured	Non-ruptured	Gram Positive Septicemia
No.	14	22	2	20	14	5	5
Av. Age	61 days	62 days	7.5 yrs	8.075 yrs	9.7 yrs	11.2 yrs	6 days through 4 yrs
% Pos Blood Culture	100	0	100	0	0	0	100
% Pos Limulus Assay	64	19	50	0	14.3	0	0
% Pos Staph Clumping	50	19	100	11	0	20	0
% Pos Protamine Sulfate	50	27	50	35	65	20	100
WBC	8,596	14,485	22,250	12,715	13,000	10,700	18,700
Platelet Count	67,393	257,394	35,000	323,800	335,857	294,400	299,800

White Blood Cell Count. Babies with septicemia had an average white blood count of 8,596, with a range of 2,050 to 29,400. Non-infected babies had an average white blood count of 14,520, with a range of 7,800 to 35,000. Forty-two per cent of the babies with positive blood cultures had a white blood count below 5,000; while none of the babies with negative blood cultures had a count below 5,000. The white blood count was significantly lower in the babies with bloodstream infection ($P < 0.05$).

Platelet Count. Babies with gram negative septicemia had a significantly lower platelet count than non-septic infants ($P < 0.001$). The babies with positive blood cultures had an average platelet count of 67,393 (S.D. = 41,500). Non-infected postoperative babies had an average platelet count of 257,394 (S.D. = 72,087). One hundred per cent of the babies with proven gram negative septicemia at the time of the positive blood culture had a platelet count below 150,000 and 71% had a platelet count below 100,000. The lowest count was 11,000. None of the non-infected babies had a platelet count below 150,000.

Groups 3 and 4: Children with and without gram negative septicemia

There were only two children with gram negative septicemia. The limulus lysate and protamine sulfate were positive in one of the patients, and the straphylococcal clumping test positive in both. The white blood cell counts were 25,000 and 19,500; the platelet counts 50,000 and 20,000.

Of the twenty children with an average age of 8.075 years who had major trauma or operation, all had negative blood cultures and limulus lysate assays. Eleven per cent had positive staphylococcal clumping tests and 35% positive protamine sulfate tests. The average white blood count was 12,715. None were below 7,000. All platelet counts were above 150,000. The average platelet count was 323,800 (S.D. = 102,000).

Groups 5 and 6: Children with ruptured and non-ruptured appendicitis

There were 14 patients with ruptured appendicitis. The average age was 8.075 years. Five patients had non-ruptured appendicitis; the average age was 11.2 years. There were no positive blood cultures in either group. Of the patients with ruptured appendicitis, 14.3% had a positive limulus lysate test, while none of the patients with non-ruptured appendicitis had a positive assay. The staphylococcal clumping test was negative in all patients with ruptured appendicitis, but there was a 64% positive protamine sulfate test. One of the 5 patients (20%) with non-ruptured appendicitis had a positive staphylococcal clumping and protamine sulfate test. The average white blood cell count in the ruptured appendicitis group was 13,000; 11,700 in the non-ruptured group. The platelet count was similar in both groups—335,857 in the ruptured group and 294,000 in the non-ruptured group. None of the patients had a platelet count under 150,000.

Group 7: Infants and children with gram positive septicemia

There were five patients, 6 days to four years of age, who had positive blood cultures for gram positive organisms. These organisms were *Staphylococcus aureus* and *epidermidis*. None of the patients had a positive limulus lysate assay or staphylococcal clumping test. All had a positive protamine sulfate test. The average white blood count was 18,700 and none were below 7,000. The average platelet count was 299,800 (S.D. = 148,000). None were below 150,000.

Serial Platelet Counts:

Group 7: Eleven babies, average age 3 weeks, with proven gram negative septicemia had platelet counts from admission to discharge or death. Several observations were made:

1) The platelet count fell rapidly with gram negative septicemia (Figs. 1 and 2). The greatest decrease was

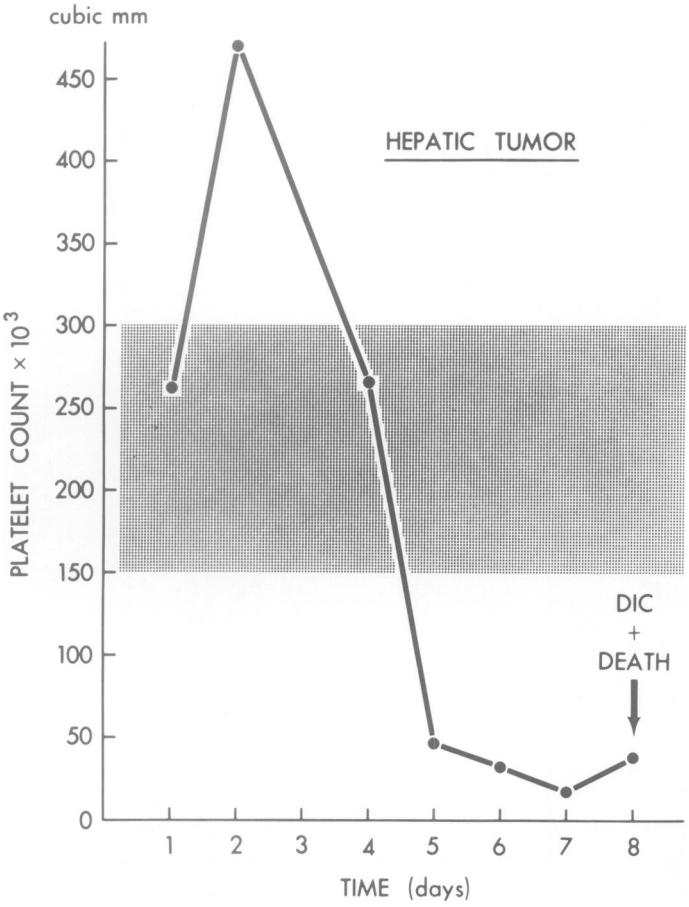

FIG. 1. Serial platelet count on 2-month old baby after extended right lobe hepatectomy. There is a marked fall in platelet count from 267,000 to 45,000 in 24 hours with the development of Klebsiella septicemia.

from 267,000 to 45,000, a fall of 222,000 in 24 hours. This patient was 2 months old and developed gram negative septicemia following extended right lobe hepatectomy for a liver tumor. Two patients had a fall of 100,000 in 12 hours.

2) An extremely low platelet count was not necessarily a grave prognostic sign (Figs. 3 and 4). Several patients survived whose platelet count during the course of gram negative septicemia fell as low as 15,000.

3) Effective treatment of septicemia resulted in a gradual rise in platelet count (Fig. 4). The increase in platelet count was a favorable prognostic sign. Although platelet counts were noted to fall over 100,000 in 12 hours, the return to over 150,000 took several days. The most rapid return occurred in four days and the slowest in 16 days. The rise in platelet count tended to be irregular, rising and falling over the course of several days with an overall trend towards an increased count.

Discussion

The limulus lysate assay described by Levin and Bang[11] in 1964 has been used to detect gram negative bacteremia and endotoxemia. The lysate from the amebocyte of the horseshoe crab, Limulus polyphemus, was found to gel when exposed to minute amounts of endotoxin. Levin and his associates[13] reported that 71% of patients with a positive blood culture for gram negative bacteria had a positive limulus test. Reinhold and Fine[17] found that concentrations of endotoxin as small as 0.002 micrograms/ml of plasma produced a positive test. However, only 2 of 18 patients with gram negative bacteremia had a positive limulus t test in a study of Martinez, Quintiliani and Tilton.[15] Stumacher, Kovnat and McCabe[19] reported that 43% of patients with gram negative bacteremia had a positive limulus lysate assay, but 36% of patients with gram positive septicemia also had a positive assay. In a study of 89 pediatric cancer patients, Feldman and Pearson[8] found a 7% positive limulus test in patients with gram negative septicemia. Our study showed a high incidence of positive tests—64%—in patients with positive blood cultures for gram negative bacteria. None of the patients with gram positive septicemia had a positive assay. Four of 41, or 10%, of infants and children who had negative blood cultures and no evidence of infection, had a positive limulus lysate assay. Variability of results among investigators may stem from the differences in extraction and preparation of the lysate or contamination of the specimen during the collection or performance of the test. Das and Folkman[6] suggested another reason for negative limulus lysate assay in patients with gram negative septicemia. They pointed out that endotoxin appears to be cleared by platelets and that more accurate and consistent results could be obtained

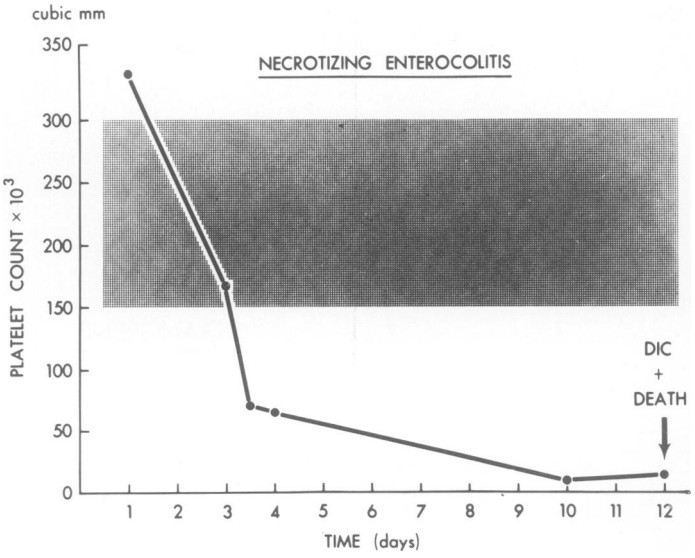

FIG. 2. Two-week old premature infant with necrotizing enterocolitis. At time of diagnosis, platelet count was normal, gradually fell over 48 hours, then at the time of perforation, fell 100,000 in 12 hours. Positive blood culture at that time.

by performing the limulus lysate assay on the platelet fraction of plasma. With this technique, they obtained positive tests in 16 of 18 patients with gram negative bacteremia or localized gram negative infections.

The limulus lysate assay in the present study had a fairly high degree of accuracy in detecting gram negative septicemia. However, there were false positives and negatives. The test presents practical difficulties, which limits its general clinical usefulness. It is not at present commercially available as a diagnostic test. The assay requires an experienced technician and precise technique for accurate results.

Gram negative septicemia may produce some degree of intravascular coagulation without the usual clinical and laboratory signs of disseminated intravascular coagulation. By quantitative measurements of fibrin degradation products, we reasoned that early gram negative septicemia may be detected. The protamine sulfate and straphylococcus clumping tests were chosen as a quantitative method of detecting fibrin degradation products.

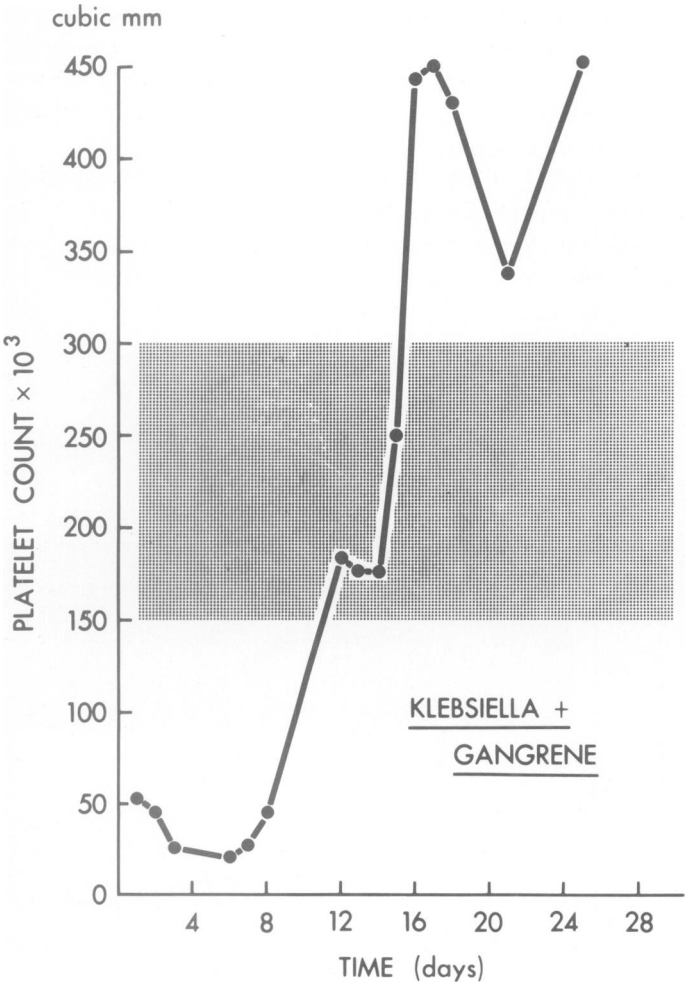

FIG. 3. Two-month old infant with gangrene of the lower leg and septicemia on admission. Platelet count was 21,000, but rose to over 150,000 in 6 days with effective treatment.

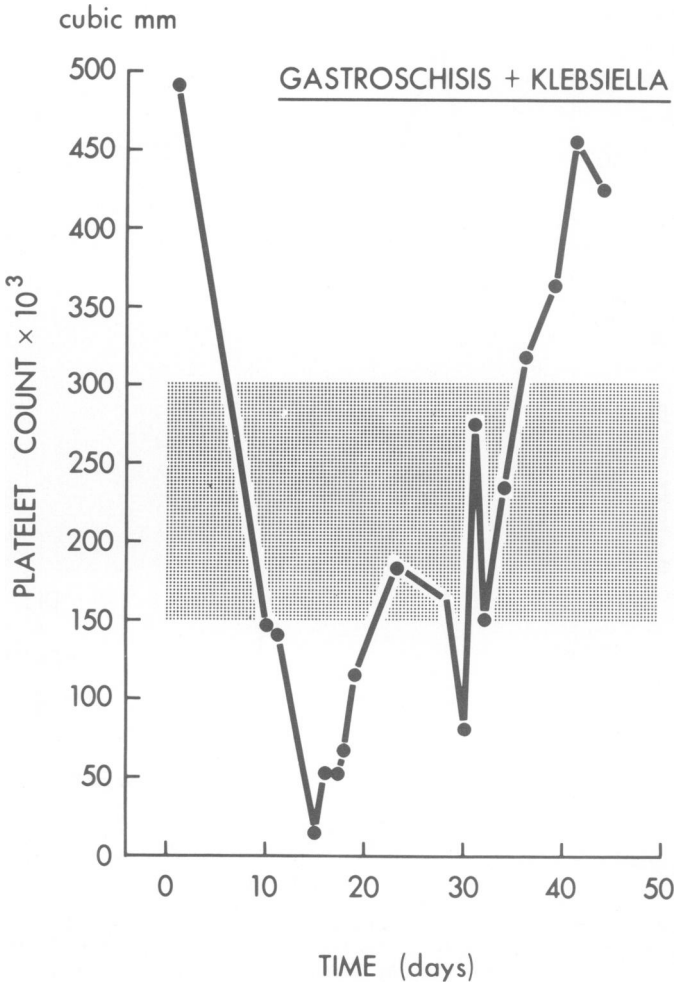

FIG. 4. Newborn infant with gastroschisis developed septicemia postoperatively. Platelet count fell to 11,000 and then climbed irregularly with treatment over a period of 16 days.

At least one of these two tests was positive in 79% of the babies with gram negative bacteremia, but 32% of babies and 35% of children with major trauma or operation had at least one test positive for degradation products. The test was also frequently positive in patients with gram positive septicemia. Positive tests for fibrin degradation products have also been noted by several investigators[4,18,20] in patients without evidence of infection or disseminated intravascular coagulation. There is an incidence of 17-25% positive tests in patients undergoing major surgery. These products have also been found in healthy newborn infants. It appears that tests for fibrin degradation products are not specific enough to serve as an aid in the early detection of gram negative septicemia in pediatric surgical patients.

Of the tests studied, we found that the most rapid, simple and accurate method for the early detection of gram negative septicemia appeared to be serial platelet counts. All the infants and children with positive blood cultures for gram negative bacteria had a platelet count

below 150,000. None of the infants or children with a negative blood culture, ruptured or non-ruptured appendicitis, or gram positive septicemia had platelet counts below 150,000. In 1973, Beller and Douglas[1] also found thrombocytopenia associated with gram negative septicemia. Eleven patients with abortions, negative endotoxin tests and blood cultures had platelet counts above 180,000. The platelet counts were below 150,000 in 7 patients that were febrile, and had bioassays positive for endotoxin. Three of these 7 patients had positive blood cultures for gram negative bacteria. Corrigan[5] studied 46 infants and children with gram positive and negative septicemia. These patients were all suffering from medical rather than surgical illnesses and none required operation. Fifty-five per cent of patients with a positive blood culture for gram negative bacteria and 71% of the patients with positive blood culture for gram positive bacteria had a platelet count below 150,000. In contrast, in our study, the average platelet count was 299,800 in patients with gram positive septicemia. None were below 150,000.

Experimental evidence suggests that the thrombocytopenia found with gram negative septicemia is the result of interaction between platelets and endotoxin. It has been suggested that endotoxin reacts with platelets, resulting in platelet aggregation. The aggregates are then trapped in microcirculation and vasoactive substances are released into the plasma. The effect of platelet microemboli and vasoactive substances are thought to account for some of the clinical and pathological findings in gram negative septicemia. Davis, Meeker and McQuarrie[7] demonstrated thrombocytopenia and platelet aggregation in rabbits injected with endotoxin. Similar results were obtained in rabbits by Beller, Graeff and Gorstein.[2] Das and Folkman[6] demonstrated that endotoxins appeared to be bound to the platelet fraction of plasma in patients with gram negative septicemia. Nagayama, Zucker and Beller[16] produced platelet aggregation *in vitro* by adding endotoxin to rabbit blood. However, endotoxin plus human blood did not lead to platelet aggregation. It appears that other factors must be present in human serum for platelets to react with endotoxin and result in aggregation. Lewis and Dickson[14] produced platelet aggregation in a Ruman blood-endotoxin mixture by adding copper. They suggested that the concentration of copper increased during infection.

The evidence suggesting platelet aggregation as the basis for thrombocytopenia found in patients with gram negative septicemia is supported by our data. The rapid fall in platelet count with gram negative septicemia, as much as 222,000 in 24 hours, suggests that thrombocytopenia is not the result of decreased platelet production, but either destruction or trapping of platelets. The low platelet count does not appear to result from consumption as part of disseminated intravascular coagulation, since only two of 18 patients with gram negative septicemia had clinical or autopsy evidence of disseminated intravascular coagulation and 21% of the babies with thrombocytopenia and positive blood cultures for gram negative septicemia had negative tests for fibrin degradation products.

We believe that the following recommendations will improve the management of pediatric surgery patients who are at high risk to develop gram negative septicemia.

1) Patients at risk should be monitored by serial platelet counts. This can be done in most hospital's clinical laboratory, using an electronic counter.

2) A fall in platelet count suggests gram negative septicemia. A source of infection should be sought and multiple blood cultures drawn. Removal of intravascular catheters and discontinuance of total parenteral feedings and the initiation of antibiotic therapy should be considered.

3) A fall in platelet count below 150,000 is strong presumptive evidence of gram negative septicemia. If even minimal clinical signs are present, antibiotics should be administered and other steps taken to combat infection.

4) A rise in platelet count suggests effective therapy for gram negative septicemia.

5) A fall in or a persistently low platelet count over several days suggests ineffective therapy. Sources of continued infection should be sought and the antibiotic program changed.

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Discussion

Dr. Basil A. Pruitt, Jr. (San Antonio): I'd like to compliment Dr. Rowe and to provide some corroborative evidence that thrombocytopenia may be a good index of infection in adult patients.

In our burn patients, looking at indices of coagulation deficits, we've found that in those with DIC fibrinogen was low, as were the platelets, but that in just/infected patients, platelets also fell. We took this problem to the laboratory and in the infected burned animal, as opposed to the uninfected burned animal, platelets are statistically depressed from the earliest postburn time on.

We also noted as did Dr. Rowe that the fibrin degradation products were not definitive as a means of separating the infected from the uninfected burns.

We have also studied the standard euglobulin lysis time which was significantly prolonged and, more specifically, we have examined a fibrinogen plus plasminogen clot lysis system with added thrombin. Findings in the infected model of a markedly prolonged clot lysis time are indicative of an anti-plasmin activity.

Further evidence for anti-plasmin in the infected preparation is on the next slide showing the suppression of plasminogen in a streptokinase activated plasminogen assay.

I would like to ask Dr. Rowe whether the fibrin split product levels in his patients rose or fell after therapy, since an increase would suggest the presence of an anti-plasmin activity?

Again, I compliment Dr. Rowe on calling our attention to a rapid means to identify that one is dealing with a significant negative infection.

Dr. M. I. Rowe (Closing discussion): I'd like to thank Dr. Pruitt for his remarks.

We agree that the thrombocytopenia that develops as a result of gram negative septicemia is not a part of disseminated intravascular coagulation.

Thirty-one per cent of the patients who had thrombocytopenia had negative quantitative tests, for fibrin degradation products.

Only two of the patients with gram negative septicemia in our series developed DIC who had thrombocytopenia. The most chilling aspect was that because of the low platelet counts, we got nervous and gave them massive platelet transfusions and those patients rapidly developed disseminated intravascular coagulation and those were two of our mortalities.