Hypothesis: Although elevations in white blood cell count (WBC) and platelet count (PC) after splenectomy for trauma constitute a physiologic event, certain WBC and PC patterns help differentiate patients with from those without sepsis.

Design: Medical record and trauma registry record retrospective review.

Setting: Academic level I trauma center.

Patients: From February 1997 through May 2001, 118 trauma patients underwent splenectomy. Sixty patients developed postoperative sepsis (pneumonia, abdominal infection, septicemia, or severe urinary tract infection) (septic group) and 58 did not (nonseptic group).

Main Outcome Measures: White blood cell count, PC, and PC/WBC.

Results: After the fifth postoperative day, the WBC of patients with sepsis remained consistently greater than $15 \times 10^9/\mu L$ and the PC/WBC remained consistently less than 20. In patients without sepsis, these values remained less than $15 \times 10^9/\mu L$ and greater than 20, respectively. Stepwise regression analysis identified 3 independent predictors of sepsis: (1) day 5 PC/WBC less than 20, (2) Injury Severity Score greater than 16, and (3) day 5 WBC greater than $15 \times 10^9/\mu L$. According to a statistical prediction model, the probability of sepsis when all 3 predictors were present was 97.4%; when all 3 were absent, it was 2.5%.

Conclusions: At and after the fifth postoperative day, a WBC greater than $15 \times 10^9/\mu L$ and a PC/WBC less than 20 are highly associated with sepsis and should not be considered as part of the physiologic response to splenectomy. In view of the seriousness of postsplenectomy sepsis, these values may be used to increase vigilance and prompt early aggressive treatment.

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During the last decade, nonoperative management has become the primary method of preserving the spleen.1 Splenectomy is still required for approximately 50% of splenic injuries.1,2 Sepsis following splenectomy is the most feared postoperative complication.3,4 Overwhelming postsplenectomy infection is a syndrome associated with a high mortality.5,6 Besides prevention, the best response to postsplenectomy sepsis is early diagnosis and treatment. The white blood cell count (WBC) is an integral part of the diagnosis of sepsis. Early trends in WBC alert the physician about the possibility of sepsis and allow prompt therapeutic response.

However, the postsplenectomy diagnosis of sepsis based on WBC elevation is confounded by the fact that leukocytosis is a physiologic response to splenectomy, similar to the phenomenon of postsplenectomy platelet count (PC) elevation.8,9 Previous reports suggest that the WBC postsplenectomy in patients with sepsis is greater and more persistent than the WBC in patients without sepsis.9,10 However, specific values that can be used at the bedside to distinguish between a “normal” and “pathologic” WBC elevation are lacking.

We hypothesized that such cutoff values exist. Additionally, we explored the use of a single number combining information related to the WBC and PC and therefore created the PC/WBC ratio. The objective of this study was to define specific WBC and PC/WBC values that distinguish patients with sepsis from patients without sepsis, early after splenectomy for trauma. An additional objective was to define indepen
PATTERNS AND METHODS

The medical records and trauma registry records of all patients who underwent splenectomy for trauma at the Los Angeles County and University of Southern California Medical Center (Los Angeles) from February 1997 to May 2001 and survived for more than 5 days were reviewed. During this retrospective study, our level 1 trauma center was run by 7 dedicated trauma/critical care attending surgeons who provided 24-hour in-house coverage. The study patients were divided into 2 groups: septic and non-septic. Patients with sepsis had any of the following postoperative complications: abdominal abscess, pneumonia, septicemia, and urinary tract infection. Standard Centers for Disease Control definitions were used for these complications.12

Data were collected on patient demographics, injury severity (by means of the Injury Severity Score [ISS] and the 6 Abbreviated Injury Scores [AIS]), associated injuries, morbidity, mortality, and hospital stay. Information was also collected on daily WBC, PC, and PC/WBC up to postoperative day 10. We did not collect information after day 10 because many patients were discharged, decreasing the sample size significantly. Continuous data were compared between patients with and without sepsis using Mann-Whitney rank sum tests and categorical data using the Yates corrected $\chi^2$ or 2-tailed Fisher exact tests. Continuous variables, such as age, ISS, AIS, estimated blood loss, fluid resuscitation, and blood transfusion, were converted to dichotomous variables by using clinically important cutoff points. Analysis of variance for repeated measures was used to investigate the difference between the 2 groups over time for each parameter. Compared variables with $P<.2$ in the univariate analysis were entered into stepwise logistic regression to identify independent risk factors for infection. The odds ratios (ORs) and 95% confidence intervals (CIs) of each independent risk factor were calculated. The independent risk factors were used to design a statistical model estimating the likelihood of infection according to the presence or absence of these factors. Finally, graphs were drawn, representing the daily mean values of the WBC, PC, and PC/WBC of the septic and nonseptic groups. Based on these graphs, specific values were selected to differentiate the 2 groups. A level of $P<.05$ was used to declare statistical significance for all comparisons.

RESULTS

A total of 118 patients were included in the study, almost equally split between the septic (58 patients) and nonseptic (60 patients) groups. The following septic complications were recorded: pneumonia (44 patients), septicemia (33), intra-abdominal abscess (21), and severe urinary tract infection (14). These complications occurred between the 5th and 43rd postoperative days (median, 7 days). Nine patients (8%) died. In 3 (1 septic, 2 nonseptic), severe head injuries resulted in brain death. Three more patients in the septic group died of multiorgan failure. One patient from each group died of pulmonary embolism. Finally, 1 patient in the nonseptic group had a massive stroke following a non–operatively treated blunt carotid artery injury.

PATTERNS OF WBC, PC, AND PC/WBC ELEVATION

There was a clear difference between patients with and without sepsis in WBC, PC, and PC/WBC, as shown in Figures 1, 2, and 3. In Figure 1, the WBC curves separate early (between postoperative days 2 and 3) but become distinctly different at day 5. At and after day 5, the mean WBC values of patients with sepsis are consistently greater than $15 \times 10^3/\mu$L. In contrast, the mean WBC values of patients without sepsis, after a temporary peak on postoperative day 2, follow a mild but progressive decline until postoperative day 6 and stabilize thereafter to a value slightly greater than $10 \times 10^3/\mu$L. Similarly, in the PC/WBC curves of Figure 3, patients with sepsis have values less than 20, whereas patients without sepsis have values consistently greater than 20 after the fourth postoperative day. The difference between WBC mean values becomes statistically significant on the fifth postoperative day, whereas the mean values of PC and PC/WBC became statistically significantly different on the second postoperative day. In general, the fifth postoperative day shows a good discriminatory ability to distinguish between patients with and without sepsis based on the WBC and PC/WBC. When the data were analyzed by type of postoperative complication, similar trends between patients with and without sepsis were observed in the subgroups.
On comparison of patients with and without sepsis, statistically significant differences were found in ISS, estimated blood loss, volume of fluid resuscitation and blood transfusion preoperatively and intraoperatively, and the incidence of pelvic and lower extremity fractures (Table 1). On stepwise logistic regression, 3 variables were identified as independent risk factors of sepsis: day 5 PC/WBC less than 20 (OR, 10.5; 95% CI, 3.3-33.7; P = .002), ISS greater than 16 (OR, 15.2; 95% CI. 3.3-116; P = .001), and day 5 WBC greater than 100,000/mm³ (OR, 15.2; 95% CI, 3.3-116; P = .001). The following statistical model was designed to predict sepsis based on the 3 independent risk factors: log odds of sepsis = -3.65 + (2.72 × [ISS>16]) + (1.87 × [day 5 WBC>100,000/mm³]) + (2.35 × [day 5 PC/WBC<20]), where 1 is used when the condition is true and 0 when the condition is not true. The probability of sepsis based on this model is presented in Table 2. If all 3 independent risk factors are present, the probability of sepsis is greater than 96%; if all are absent, the probability is less than 3%. The probability of sepsis is greater than 50% when any 2 of the 3 risk factors are present. In particular, when day 5 WBC is greater than 100,000/mm³ and day 5 PC/WBC is less than 20, the probability of sepsis is greater than 99%. Therefore, the differences in mean platelet count values are significant when the 95% CIs between the 2 groups do not overlap. Therefore, the differences in mean PC/WBC ratio become significant after the second postoperative day.

RISK FACTORS FOR SEPSIS

Table 1. Comparison of Patients With and Without Sepsis Following Posttraumatic Splenectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Septic (n = 60)</th>
<th>Nonseptic (n = 58)</th>
<th>P  Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>38 ± 17</td>
<td>34 ± 16</td>
<td>.15</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>43 (74%)</td>
<td>46 (77%)</td>
<td>.83</td>
</tr>
<tr>
<td>Penetrating trauma, No. (%)</td>
<td>26 (43%)</td>
<td>21 (36%)</td>
<td>.43</td>
</tr>
<tr>
<td>ISS</td>
<td>27 ± 12</td>
<td>20 ± 10</td>
<td>.002</td>
</tr>
<tr>
<td>Head injury, No. (%)</td>
<td>10 (17%)</td>
<td>6 (10%)</td>
<td>.42</td>
</tr>
<tr>
<td>Pulmonary injury, No. (%)</td>
<td>22 (37%)</td>
<td>17 (29%)</td>
<td>.44</td>
</tr>
<tr>
<td>Colon injury, No. (%)</td>
<td>8 (13%)</td>
<td>4 (7%)</td>
<td>.36</td>
</tr>
<tr>
<td>Pancreatic injury, No. (%)</td>
<td>14 (23%)</td>
<td>9 (16%)</td>
<td>.35</td>
</tr>
<tr>
<td>Other abdominal injury, No. (%)</td>
<td>39 (65%)</td>
<td>30 (52%)</td>
<td>.24</td>
</tr>
<tr>
<td>Pelvic or lower extremity fractures, No. (%)</td>
<td>14 (23%)</td>
<td>5 (9%)</td>
<td>.04</td>
</tr>
<tr>
<td>Estimated blood loss, mL</td>
<td>2381 ± 2013</td>
<td>1635 ± 1354</td>
<td>.02</td>
</tr>
<tr>
<td>Fluid resuscitation, mL</td>
<td>5961 ± 3602</td>
<td>4577 ± 4165</td>
<td>.004</td>
</tr>
<tr>
<td>Blood transfusion, U</td>
<td>6 ± 5</td>
<td>3 ± 3</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 2. Probability of Sepsis Based on the 3 Independent Predictors of Sepsis

<table>
<thead>
<tr>
<th>PC/WBC &lt;20</th>
<th>WBC &gt;15 ×10³/μL</th>
<th>ISS &gt;16</th>
<th>Probability of Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>0.964</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>0.804</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0.719</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>0.638</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0.282</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>0.213</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>0.144</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0.025</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. ISS indicates Injury Severity Score; WBC, white blood cell count; and ICU, intensive care unit.

*PC indicates platelet count; WBC, white blood cell count; and ISS, Injury Severity Score.
The phenomenon of temporary leukocytosis following splenectomy has been well known for many decades as a physiologic response to the removal of the spleen.® Ironically, leukocytosis is also a prominent finding of postoperative sepsis, a common and much feared complication of splenectomy. Therefore, confusion exists as to whether postsplenectomy leukocytosis should be considered a normal finding or a warning sign mandating treatment.

Previous reports have shown a difference in the magnitude and persistence of leukocytosis between patients with and without sepsis after splenectomy. Sekikawa and Shatney 3 found that from the 6th to the 10th postoperative day, most patients with sepsis had leukocyte counts greater than 20 × 10³/µL vs patients without sepsis with counts less than 17 × 10³/µL. Similarly, Rutherford et al 10 suggested that a leukocyte count greater than 20 × 10³/µL after the 10th postoperative day should initiate a vigorous search for infection. One could argue that the significance of leukocytosis should be determined much earlier than the 10th postoperative day; by then, sepsis is usually overt and the chance for early treatment is lost.

In our study, we tried to determine the earliest postoperative day that a specific WBC predicts the development of sepsis. A WBC greater than 15 × 10³/µL at and after the fifth postoperative day emerged as a reliable predictor of sepsis. Our findings are in agreement with those of Horowitz et al, 8 who found that following posttraumatic splenectomy, 18 infected patients had a WBC greater than 16 × 10³/µL compared with 24 noninfected patients with a WBC less than 16 × 10³/µL.

In addition to WBC, we also examined the PC/WBC ratio. This is a novel method to distinguish between normal response and infection by incorporating the changes of WBC and PC. Thrombocytosis is a physiologic response to splenectomy. 12,13 Thrombocytopenia is a physiologic response to sepsis due to increased platelet adhesiveness and consumption. 14,15 The combination of splenectomy and sepsis may lead to a milder increase of the platelet count. The same combination leads to an augmented leukocytotic response. Therefore, we hypothesized that PC/WBC postsplenectomy may be lower in patients with sepsis than in patients without sepsis. A PC/WBC less than 20 at and after the fifth postoperative day reliably identified patients who developed sepsis; patients with a PC/WBC ratio greater than 20 usually did not have sepsis.

The stepwise logistic regression identified both the WBC and PC/WBC ratio as independent predictors of sepsis. As expected, the combination was a better predictor than either one individually. At the fifth postoperative day, if the WBC is greater than 15 × 10³/µL and the PC/WBC ratio is less than 20, the probability of sepsis is—according to our prediction model—greater than 80%. If both are absent, the probability is less than 15%. The addition of an ISS greater than 16 to this model proves its predictive ability. In the presence of all factors (ISS, WBC, and PC/WBC ratio), more than 96% of patients developed sepsis; in the absence of all factors, only 2.5% did so. Given that overt clinical symptoms of sepsis usually appeared after the seventh postoperative day, the WBC and PC/WBC ratio at the fifth postoperative day may function as early and useful indicators to start therapy.

Our study is limited by its retrospective design, particularly as related to the determination of the presence of sepsis and the description of its severity. To have statistically meaningful sample sizes, we lumped all infectious postoperative complications together, regardless of their type and severity. Clearly, all pneumonias are not the same. We also did not take into account the clinical history. Physicians make decisions by integrating information obtained from physical examination and laboratory and imaging tests. The WBC and PC/WBC ratio should never be viewed in isolation as the sole determinants of the presence of sepsis. Finally, information was collected only up to the 10th postoperative day. After this day, the sample size decreased dramatically because most patients without sepsis were discharged.

The purpose of the study was to identify early predictors of sepsis. We believe that by the fifth day following posttraumatic splenectomy, 2 easily derived variables, the WBC and PC/WBC ratio, may help the physician confirm the development of sepsis and the need for treatment. If the WBC is greater than 15 × 10³/µL and the PC/WBC ratio is less than 20 on that day, particularly in patients with ISS greater than 16, the physician should seriously consider treatment by empiric antibiotics and further diagnostic work-up to prevent the untoward sequelae of postsplenectomy sepsis.

This paper was presented at the 73rd Annual Meeting of the Pacific Coast Surgical Association, Las Vegas, Nev, February 17, 2002, and is published after peer review and revision. The discussion is based on the originally submitted manuscript and not the revised manuscript.

Corresponding author: George C. Velmahos, MD, Los Angeles County and University of Southern California Medical Center, 1200 N State St, Room 9900, Los Angeles, CA 90033 (e-mail: velmahos@usc.edu).

REFERENCES


DISCUSSION

William Schecter, MD, San Francisco, Calif: The spleen is an enigma. Yehuda Halevy, a 12th-century poet writing in Hebrew, stated that the function of the spleen is to cleanse both the blood and spirit of unclean and obscure matter. Nine hundred years later, Dr Velmahos and his colleagues have studied the effects of splenectomy on the clearance of platelets, leukocytes, and by extension, bacteria from the circulation. Specifically, they hypothesized that leukocytosis above a certain level could serve as a marker for bacterial infection despite the known physiologic leukocytosis following splenectomy. They describe a novel ratio of platelet to leukocyte counts that serves as a control for decreased clearance of senescent leukocytes by comparing them to platelets. The ratio is perhaps made more sensitive by the relative thrombocytopenia, which sometimes accompanies infection. They concluded that on postoperative day 5, a white blood count greater than 15000 cells per cubic millimeter, a platelet to white blood count ratio less than 20, and an injury severity score of greater than 16 are all associated with a high probability of infection. I agree with their conclusions and admire the authors’ creativity in devising the platelet to white blood cell ratio.

However, several points in their paper deserve comment.

1. The infection rate of almost 30% is extraordinarily high. Dr Jan Horn and I reported an overall infection rate of 22% after splenectomy and splenorrhaphy in a paper presented before this organization in 1993. Others have reported infection rates varying between 26% and 30%. The 17% intra-abdominal abscess rate and the 28% bacteremia rate are also very high. Most of the infections (37%) were described as pneumonia. Can the authors explain why they observed such a high infection rate? How did the authors retrospectively identify patients with pneumonia given the great difficulty in distinguishing pneumonia from acute lung injury in trauma patients? I was surprised to see no comment in the manuscript regarding postoperative wound infection. Did any occur?

2. The physiologic response to significant trauma, even in the absence of splenic injury, often involves leukocytosis and immunosuppression characterized by a fall in the absolute lymphocyte count. This process, presumably mediated by cytokines, can progress to the systemic inflammatory response syndrome even in the absence of bacterial infection. The authors did not report data on the differential white blood count. Physiologic leukocytosis due to splenectomy should be accompanied by an increase in lymphocytes. Do you have any data comparing the absolute lymphocyte count with the neutrophil count, which might shed some light on the role of immunosuppression in these patients?

3. Although the infected patients received twice as much blood as the uninfected patients, blood transfusion did not fall out as an independent variable for infection on stepwise regression analysis. This finding is in contrast to the findings of our 1993 study, which was titled “Transfusion Significantly Increases the Risk of Infection after Splenic Injury.” Others have also noted the immunosuppressive effect of blood transfusion and its association with infection. Could the authors speculate on the discrepancy between these findings?

4. Finally, I should make some comment about the function of these senescent neutrophils. Could their senescence mean that they are less effective at destroying bacteria, or worse, could their oxidative enzymes be directed at self, increasing the risk of systemic inflammatory response? Unfortunately, a clinically useful test of neutrophil function has yet to be developed.

John T. Owings, MD, Sacramento, Calif: I have a question for you specifically about your methods. It appeared that you derived the idea of using the platelet to WBC ratio as well as the white count and the ISS from a population of patients and then did a logistical regression analysis on the same group. Did you do the regression on the same population from which you derived these ideas, and if you did, have you considered applying it to a different population in order to validate the method? If you don’t, obviously what you will get is a self-fulfilling prophecy.

David G. Greenhalgh, MD, Sacramento: In burn patients, a dropping platelet count is a very important factor in predicting sepsis, where the white count isn’t very helpful. You’ve done the analysis looking at the change in white blood cell count and the ratio. Why not just look at the change in platelets itself? Is that the real key factor here in that you don’t have an increase in platelets that you normally have, so if you could look at just the change in platelets from day of splenectomy until day 5 as a predictive factor?

M. Atik, MD, Idyllwild, Calif: I am intrigued by this ratio of the platelet counts to the leukocytes. This fall in this ratio clearly is affected either by a decrease in the platelet count or by an increase in the leukocytes. I wonder if the authors have noted a disproportionate decrease in the platelet counts in at least some of their patients, and if that is correlated with the severity of infection. If so, it further supports the role of platelets in the outcome of infection. As you know, in response to infection in sepsis, platelet adhesion and aggregation is increased. The platelet sampling is decreased as they are sequestered in the microcirculation, leading to impaired perfusion and even in multiple organ failure and possibly DIC (diffuse intravascular coagulopathy) when infection and sepsis is severe enough. Would the author please comment also on the marked differences in the number of transfusions between the infected and the noninfected patients as transfusion. Multiple transfusions also suppress the platelets, and that affects the ratio between the platelet and the white blood cell counts, contributing to the severity of an infection.

John C. Mayberry, MD, Portland, Ore: No longer when I am rounding with the residents can we just write off the elevated white blood cell count in a splenectomized patient. However, I do have a question similar to Dr Owings about how exactly the multiple regression analysis was done and what variables were included. For example, was fever included? There is a paper by I believe it is Michael Chang published in the last couple of years which showed that in all trauma patients, not just splenectomized trauma patients, the white blood cell count was not accurate. However, fever was accurate.

There are also other signs of infection. For example, vital signs, heart rate, blood pressure, other signs of sepsis. Patients with pneumonia have sputum development. They have an infiltrate on chest x-ray. So whether or not this is actually a useful test is another question. For example, were there really patients who had no other signs of infection besides a white blood cell count greater than 157?
Dr Velmahos: One of Dr Schecter’s first questions was why was the infection rate so high. The only reason that I can think is that most of these patients did not have isolated splenic injuries. They were critically injured patients. In these patients the infection rate is expected to be very high.

How did we identify retrospectively pneumonia? A major limitation of our study relates to its retrospective design; obviously we tried to do our best to define pneumonia according to standard CDC criteria. We didn’t include wound infection because we wanted to bother only with deep-seated infections that need something more than just a simple surgical maneuver for cure. In wound infections, all one needs to do most of the time is take a few staples out as opposed to pneumonia, blood sepsis, where one needs intensive treatments.

We obviously are aware of the differences and the similarities between SIRS and sepsis and we tried as best as we could to make that distinction through this retrospective study. Obviously we qualified for sepsis only when a positive blood culture was present.

Why was the blood transfusion kicked out from the stepwise regression analysis? This is just the nature of the statistical result, and I believe that in the stepwise regression you try to identify independent risk factors. It seems like a high Injury Severity Score was intimately correlated with the amount of blood transfusions and therefore the analysis kicked that factor out and left the high Injury Severity Score of more than 16 as the independent risk factor.

Drs Owings and Mayberry, you both asked about the methodology of the statistical analysis. We first proceeded to univariate analysis. We compared every possible variable that we could think of, including temperature, in the 2 groups, infected and noninfected patients by univariate analysis. Then we selected all of those variables that had a \( P \) value of less than .2 and threw these into stepwise regression analysis, which automatically selected the independent risk factors at the level of .05 \( P \) value this time.

The platelet changed? There was a question whether we could do better just by using the platelet count change rather than the ratio. We included the platelet count in our analysis but I didn’t report these here in the sake of time. But the ratio was a much more accurate predictor of infection compared to the platelet count.

Finally, on the pathophysiology of platelets and sepsis, Dr Atik, I agree. Following splenectomy in the noninfected patients, the platelets increase in numbers. However, if the patient at the same time becomes infected, then platelets are consumed and don’t increase as much as in noninfected patients. This is the reason why the platelet counts stay relatively low following infection.

CME Announcement

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- Article-specific questions
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- Online CME questionnaire
- Printable CME certificates and ability to access total CME credits

We apologize for the interruption in CME and hope that you will enjoy the improved online features that will be available in early 2003.