CHAPTER 9

PRIMARY AND SECONDARY CHANGES IN PLATELET COUNT
AND OUTCOME IN
MEDICAL AND SURGICAL ICU PATIENTS

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Submitted
ABSTRACT

Objective: Thrombocytopenia is related to adverse outcome in critically ill patients. In many patients admitted to the intensive care (ICU), the platelet count (PC) shows an initial decrease followed by a rebound of varying amplitude. Opposed to primary changes, the relation of secondary changes of PC with outcome has not been systematically studied. In this study we have analyzed changes in a large, heterogeneous set of ICU patients. Based on the changes of PC with time we established previously, PC-changes were evaluated with a simple model that incorporates the biphasic changes in PC.

Design: Analysis of the prospectively collected EURICUS-II database.

Setting: 53 ICUs in 11 European countries.

Patients: All patients for whom PC were available.

Measurements and results: 5206 Patients were classified as medical (55%), unscheduled surgery (24%) or scheduled surgery (21%). During ICU-stay daily PC were recorded. The rate of change of PC between day 0 and 2 was expressed as $\Delta PC/\Delta t_{0\rightarrow2}$, PC on day 2 as $PC_2$ and the rate of change in PC between day 2 and 10 as $\Delta PC/\Delta t_{2\rightarrow10}$. In non-survivors $\Delta PC/\Delta t_{2\rightarrow10}$ was only $1\pm26$ versus $13\pm31 \cdot 10^9/l/d$ for survivors (p<0.001) Differences in early PC as reflected by $PC_2$ ($167\pm112$ vs. $188\pm102 \cdot 10^9/l$; p<0.001) and $\Delta PC/\Delta t_{0\rightarrow2}$ (-16±54 vs. -13±41 ·10⁹/l/d; NS) were less pronounced.

Conclusions: A low increase or even a decrease in PC after day 2 is associated with poor outcome both in medical and in surgical ICU patients. In individual patients, clinicians should bear in mind the typical time course of the PC after ICU admission in order to recognize abnormal patterns. In patient groups, taking $\Delta PC/\Delta t_{2\rightarrow10}$ into account may aid in improving outcome assessment.

INTRODUCTION

Both production and consumption of platelets are increased in diseases that involve systemic inflammation. Initial changes in PC in patients admitted to the ICU mostly concern decreases in PC. The magnitude of thrombocytopenia after ICU-admission has proven to be of important negative prognostic value in trauma [1], ruptured aortic aneurysm [2], malaria [3], meningitis [4], and sepsis patients [5], as well as in patients in general that were admitted to the ICU [6,7,8,9]. The studies that investigated PC and outcome all focused on changes in PC to subnormal values, and mostly early after ICU-admission. Whereas systemic inflammation is initially accompanied by a drop in PC, in uncomplicated patients a rebound increase in PC is observed. For example in a trauma patient who does not need prolonged ICU-support, the PC will usually start to rise 2 to 3 days after the injury and reach
supranormal levels after two weeks [10]. Increased production of platelets induced by interleukin-6, thrombopoietin and other cytokines [11] is responsible for this secondary thrombocytosis. We have noted that in critically ill patients who have an ongoing inflammatory response this rebound thrombocytosis is absent in many cases. This observation led us to the hypothesis that more severe inflammation and thus adverse outcome, may be related to an absent or blunted thrombocytotic response. In a recent study in patients admitted to a surgical ICU we found that non-survivors have a lower rate of change in PC after day 2 [10]. In the present study we attempted to systematically analyze both medical and surgical patients, early and late changes in PC, and their relation with outcome. A large multicenter database that had been prospectively collected, was used for this purpose. We hypothesized that the information provided in the secondary changes of the platelet count would be distinct from the information carried by initial changes in the platelet count. A simple mathematical model based on the time course of PC as identified earlier [10] was applied. This model (Fig. 9.1) assumes that PC decreases linearly during the first two days after ICU-admission, reaches a nadir value after two days, and changes linearly between day 2 and day 10.

Figure 9.1. Three-parameter model for time dependent changes in platelet count (PC) that was used in this study. For each patient, the rate of change in the platelet count, $\Delta PC/\Delta t$ was calculated by linear regression between day 0 and day 2 ($\Delta PC/\Delta t_{0\rightarrow 2}$) and between day 2 and day 10 ($\Delta PC/\Delta t_{2\rightarrow 10}$). Nadir PC was assumed to occur at day 2 ($PC_2$). In this example $\Delta PC/\Delta t_{0\rightarrow 2}$ equals the slope of the descending line on the left (-110 $\cdot 10^9$/l/d), $PC_2$ is the PC at day 2 (135 $\cdot 10^9$/l) and $\Delta PC/\Delta t_{2\rightarrow 10}$ equals the slope of the ascending line (+34 $\cdot 10^9$/l/d).
# PATIENTS AND METHODS

## EURICUS-II Database

The EURICUS-II dataset contains data of 53 ICUs (medical and surgical) in 11 European countries [12]. Patient data were recorded from admission to the ICU until discharge from the ICU. On admission patients were divided into one of three categories: unscheduled surgery, scheduled surgery or medical as has been described before [13]. In addition, age, the simplified acute physiology score (SAPS-II; [13]) on admission, daily PC (normal range 150-350 $10^9$/l) between day 0 (admission to the ICU) and day 10, were collected. Patients were classified into non-survivors and survivors on the basis of hospital mortality.

| Table 9.1
| Patient characteristics
<table>
<thead>
<tr>
<th>Survivors</th>
<th>Non-survivors</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4034</td>
<td>1172</td>
</tr>
<tr>
<td>Age, Years</td>
<td>59±21</td>
<td>66±18</td>
</tr>
<tr>
<td>SAPS-II</td>
<td>31±15</td>
<td>49±20</td>
</tr>
<tr>
<td>$\Delta PC/\Delta t_{0\rightarrow 2}$, $10^9$/d</td>
<td>-13±41</td>
<td>-16±54</td>
</tr>
<tr>
<td>$PC_2$</td>
<td>188±102</td>
<td>168±112</td>
</tr>
<tr>
<td>$\Delta PC/\Delta t_{2\rightarrow 10}$, $10^9$/d</td>
<td>13±31</td>
<td>1±26</td>
</tr>
<tr>
<td>Values ± SD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model of time dependent changes in PC

The platelet count was assumed to change linearly until day 2 (mostly a decrease), and to change linearly (increase or decrease) afterwards. For each individual patient three descriptors of serial changes in platelet count were extracted with a special program that calculated individual regression coefficients (Fig. 9.1):

- $\Delta PC/\Delta t_{0\rightarrow 2}$, $10^9$/d: the early rate of change of the PC, between day 0 and day 2
- $PC_2$, $10^9$/l: platelet count on day 2
- $\Delta PC/\Delta t_{2\rightarrow 10}$, $10^9$/d: the late rate of change of the PC, between day 2 and 10

Thus for each patient the course of the PC was approximated by two linear regression coefficients reflecting the rates of change ($\Delta PC/\Delta t_{0\rightarrow 2}$ and $\Delta PC/\Delta t_{2\rightarrow 10}$) and the PC on day 2 ($PC_2$) which was assumed to approximate nadir PC at any time. To verify the assumption that $PC_2$ estimates the nadir PC, $PC_2$ was compared with nadir PC.
Statistical analysis.
Means of all (derived) parameters were compared between non-survivors and survivors for the overall patient group, as well as for the three admission groups. For the various analyses which were performed, our approach was to use the largest available subsets of patients possible for each specific analysis. Thus the total number of patients used varies in the different analyses. This variation is mainly dependent upon length of stay, since the EURICUS-II study only recorded data during ICU-stay. Unless indicated otherwise standard deviations are used. The two-sided Student's \( t \)-test was used for comparison of continuous parameters, without assuming equal variances. The Bonferroni-correction was used in case of multiple testing.

RESULTS

Overall patient characteristics
20508 PC values collected between day 0 and day 10 were available for 5206 patient admissions. Of these admissions, 55% were medical, 24% unscheduled surgery and 21% scheduled surgery. Mean ICU-length of stay was 5.9±10.5 days with a median (interquartile range) value of 2 (1-6) days. The overall mortality rate was 23% (Table 9.1), with group mortalities of 36% for medical, 35% for unscheduled surgery and 11% for scheduled surgery respectively.

Platelet Counts
On admission, mean PC in the entire group was 217±115·10^9/l. At this time only 4% had a PC<50·10^9. Fig. 9.2 shows the diverging time course of the PC between non-survivors and survivors. On day 0 the non-surviving patients had a mean PC of 203±122 that dropped to 167±112 on day 2 and rose to 222±137·10^9/l on day 10. In the survivors this value at day 10 was 317±166, which is 95·10^9/l higher than in non-survivors (p<0.001). This pattern of an initial decrease with a subsequent increase was also observed in the three major subgroups: medical, unscheduled surgery and scheduled surgery, with mean PC reaching a minimal value on day 2. In support of the model’s assumption, the nadir PC showed a strong correlation with the \( PC_2 \), with a Spearman correlation coefficient of 0.89 (p<0.001).

In non-survivors \( \Delta PC/\Delta t_{2\to 10} \) was only 1±26 compared to 13±31·10^9/l/d for survivors (p<0.001). The difference in \( PC_2 \) (167±112 vs. 188±102·10^9/l; p<0.001) was less pronounced. \( \Delta PC/\Delta t_{0\to 2} \) showed no difference (-16±54 vs. -13±41·10^9/l/d; NS).
A value of $\Delta PC/\Delta t_{2\rightarrow 10}$ below $-30\cdot 10^9$/d was associated with a 40% mortality, whereas a rise of more than $+60\cdot 10^9$/d was associated with a 3% mortality. Figure 9.3 shows the distributions and associated mortalities of the three parameters $\Delta PC/\Delta t_{0\rightarrow 2}$, $PC_2$ and $\Delta PC/\Delta t_{2\rightarrow 10}$ for the three admission groups. Fig. 9.3 illustrates that in the majority of patients $PC$ indeed decreases between day 0 and day 2 in most patients, but drops to levels still over $150\cdot 10^9$/d in most patients. Only few patients have severe thrombocytopenia on day 2 and after day 2 $PC$ rises in most patients. Fig 9.3 also indicates that $\Delta PC/\Delta t_{2\rightarrow 10}$ has the clearest association with mortality.

Since $PC_2$ and $\Delta PC/\Delta t_{2\rightarrow 10}$ had the strongest relation with mortality, the interaction of these two parameters (Table 9.2) and their combined relation with mortality (Fig. 9.4) were analyzed. Here subranges were chosen to approximate interquartile ranges for the two respective parameters. The ordinal by ordinal Spearman correlation coefficient was -0.16, revealing that $PC_2$ and $\Delta PC/\Delta t_{2\rightarrow 10}$ are nearly independent. Fig. 9.4 shows that the relations of low $PC_2$ and a low $\Delta PC/\Delta t_{2\rightarrow 10}$ with mortality are additive. For example the 108 patients with $PC_2<100\cdot 10^9$/l and $\Delta PC/\Delta t_{2\rightarrow 10}<0$ have 60% mortality rate in contrast to an 8% mortality rate in the 113 patients with $PC_2>200\cdot 10^9$/l and $\Delta PC/\Delta t_{2\rightarrow 10}>30\cdot 10^9$/d.

Children

In the small subgroup of children (age <=15 year; 13 nonsurvivors; 39 survivors) only $\Delta PC/\Delta t_{2\rightarrow 10}$ showed a difference with $-9\pm 40$ versus $24\pm 40\cdot 10^9$/d (p=0.016) in non-survivors and survivors respectively.
Late mortality and early changes in PC
Since changes in PC only shortly before death might disproportionately affect $PC_2$ and $\Delta PC/\Delta t_{2\rightarrow10}$, we performed an additional analysis on the predictive value of $PC_2$ and $\Delta PC/\Delta t$ for a longer period ahead. In the subgroup of patients that had a stay of at least 10 days at the ICU, $PC_2$ and the rate of change between day 2 and day 5 (i.e. $\Delta PC/\Delta t_{2\rightarrow5}$) were compared. $PC_2$ was $184\pm124$ and $186\pm100\cdot10^{9}/l$ respectively (NS) and $\Delta PC/\Delta t_{2\rightarrow5}$ was $0\pm30$ and $10\pm32\cdot10^{9}/l/d$ respectively (p<0.001).

<table>
<thead>
<tr>
<th>$\Delta PC/\Delta t_{2\rightarrow10}$ (10^9/l/d)</th>
<th>$PC_2$ (10^9/l)</th>
<th>&lt;0</th>
<th>0 ~ 10</th>
<th>10 ~ 30</th>
<th>&gt;30</th>
<th>Totals</th>
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<tbody>
<tr>
<td>&lt;=100</td>
<td>106 (5)</td>
<td>100 (5)</td>
<td>134 (7)</td>
<td>98 (5)</td>
<td>438 (23)</td>
<td></td>
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<tr>
<td>100 ~ 150</td>
<td>107 (6)</td>
<td>99 (5)</td>
<td>127 (7)</td>
<td>87 (5)</td>
<td>420 (22)</td>
<td></td>
</tr>
<tr>
<td>151 ~ 200</td>
<td>136 (7)</td>
<td>91 (5)</td>
<td>117 (6)</td>
<td>38 (2)</td>
<td>382 (20)</td>
<td></td>
</tr>
<tr>
<td>&gt; 200</td>
<td>299 (16)</td>
<td>123 (6)</td>
<td>153 (8)</td>
<td>113 (6)</td>
<td>688 (36)</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>648 (34)</td>
<td>413(21)</td>
<td>531(28)</td>
<td>336 (17)</td>
<td>1928 (100)</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION
The relationship between PC and mortality in critically ill patients was analyzed in this study. In a large group of medical and surgical ICU patients the prognostic importance of PC extends well beyond initial changes. With regard to PC, day 2 after ICU admission can be viewed as a turning point (Fig 9.1). The extent of the decrease in PC during the first two days was not related with mortality. Many investigators observed a relation with early nadir PC and mortality. In this study we also found that the PC at day 2, which adequately reflected nadir PC, is related with mortality. But the daily rate of change in PC after day 2 showed the strongest relation with mortality. This phenomenon was especially marked in unscheduled surgery patients (Fig. 9.3), where these mortalities were 53% and 0% for low (i.e. <0) and high (>30·10^9/l/d) values of $\Delta PC/\Delta t_{2\rightarrow10}$ respectively.
Vanderschueren [6] reported that in 329 predominantly medical ICU patients that nadir PC was associated with mortality. Unfortunately, the authors do no report the time interval between measuring a nadir PC and the patients' death. Stephan observed in 147 surgical ICU patients [7] that those patients who had a PC below 100 at any time had a mortality rate of 38%, compared
with a 20% mortality rate for PC >100·10^9/l. In the latter study thrombocytopenia occurred 1.8±0.5 days after admission.

In a previous study of 1415 admissions to a surgical ICU [10] we also observed an association with mortality of a low rate of change in PC after day 2. The current study generalizes these results to a larger, more heterogeneous patient group that includes medical patients as well as children. That changes in PC between day 2 and day 5 were also associated with the mortality that occurred after day 10, underscores that the phenomenon we observed is not solely the result of changes occurring directly before death.

Limitations of this study
The primary purpose of EURICUS-II was to investigate the role of collaborative practice at the ICU, and to find parameters to measure improvements in nurse-doctor interaction [12]. Thus we retrospectively analyzed data that were prospectively collected for other purposes. The database contains very heterogeneous patients without detailed information on their condition before ICU-admission, making analysis of PC behavior in specific syndromes or diseases impossible. Especially in the medical patients, PC before ICU-admission would have been useful. Pre-admission PC would obviously allow a better estimation of ΔPC since in many cases PC will have decreased already before ICU-admission. Many relevant physiological parameters were not recorded, such as leukocyte counts or quantitative indicators of systemic inflammation (e.g. C-reactive protein). We did not study the mechanisms that lead to decreased PC. Nevertheless, as pointed out below, we think other studies provide compelling arguments to assume that inflammation-induced platelet sequestration plays a major role.

Pathophysiology of decreasing platelet counts
Decreases in PC are by definition the result of platelet consumption that is higher than platelet production. We assume that increased platelet consumption is the main contributor to (relatively) low PC in ICU patients both during the primary and secondary phases of ICU-stay. Acute PC-decreases must result from increased consumption of platelets since platelets have a normal life-span of 8 to 11 days [14]. The fact that only 4% had a PC below 50·10^9/l excludes a significant impact of patients with acquired bone marrow failure on our results, since such patients usually have a PC well below 50·10^9/l. In a study on thrombocytopenia in the surgical ICU 8 out of the 9 patients with sepsis and thrombocytopenia who underwent bone marrow examination during later phases of their ICU-stay, displayed a normocellular or hypercellular marrow with a normal number of megakaryocytes [7]. The same observation was made in 15 children with thrombocytopenia after sepsis without signs of disseminated intravascular coagulation (DIC) [15]. In our previous study in surgical ICU patients [10], non-survivors had higher leukocyte counts than survivors, which also argues against marrow failure. The most direct observation of increased platelet sequestration in trauma and sepsis patients in the ICU was seen after administration of 111Indium-labelled platelets. Increased sequestration was found in several organs including the lung, liver and gut, especially in patients with adverse outcomes [16].
Figure 9.3. Distribution of patients (upper panels) and mortality (lower panels) according to $\Delta PC/\Delta t_{0 \rightarrow 2}$ (left panels; 3843 patients), $PC_2$ (Middle panels; 2645 patients) and $\Delta PC/\Delta t_{2 \rightarrow 10}$ (Right panels; 2049 patients). Bar shades denote admission categories: scheduled surgery: gray bars; unscheduled surgery: black bars and medical: white bars.

The upper left panel shows that $\Delta PC/\Delta t_{0 \rightarrow 2}$ is negative in most patients, indicating an initial decrease in PC. The upper middle panel shows that a day 2, most patients still have a $PC > 150 \cdot 10^9/l$, and only 35 patients (1%) have a $PC < 20 \cdot 10^9/l$. The right upper panel indicates that after day 2, most patients display an increase in PC.

The lower middle and lower right panels indicate that decreased values of $PC_2$ and $\Delta PC/\Delta t_{2 \rightarrow 10}$ are associated with increased mortality. In the unscheduled surgery group with $\Delta PC/\Delta t_{2 \rightarrow 10} < -30 -10^9/l/d$ 19 patients had 53% mortality; while 37 patients with $\Delta PC/\Delta t_{2 \rightarrow 10} > 60 -10^9/l/d$ had zero mortality.

Figure 9.4. Analysis of combined relations of $PC_2$ and $\Delta PC/\Delta t_{2 \rightarrow 10}$ with mortality. Subranges for $PC_2$ and $\Delta PC/\Delta t_{2 \rightarrow 10}$ are different from Fig. 3., as they were chosen to best correspond to interquartile ranges (see Table 9.2 for distribution of patient numbers). Mortality is displayed on the vertical axis; the horizontal across axis shows four $PC_2$-categories; the depth axis shows four $\Delta PC/\Delta t_{2 \rightarrow 10}$-categories. This two-dimensional frequency distribution illustrates that $\Delta PC/\Delta t_{2 \rightarrow 10}$ has a stronger association with mortality than $PC_2$. 
The term platelet sequestration is broad enough to include the distinct process of adhesion to endothelium and aggregation in clots. Apart from the effect of systemic inflammation that is present in the majority of ICU-patients [17], blood loss [18] and intravascular coagulation [19] are frequent causes of acute decreases PC. Although sometimes acting in concert [20], these processes are separate and in most sepsis patients with thrombocytopenia significant diffuse intravascular coagulation (DIC) is not present [21]. Endothelial cell activation as part of systemic inflammation can trigger platelet adhesion by itself through the expression of a variety of adhesion molecules [22]. Platelet sequestration is also observed without DIC in several important models of systemic inflammation. In experimental models of TNF-administration [23] or malaria [24] mortality was related to the extent of thrombocytopenia, and not DIC. Experimentally and clinically it is difficult to measure the contribution of endothelial activation to platelet consumption. It is also not known if sequestration of platelets is directly causal to mortality, but the inflammatory potential of adherent or aggregating platelets is well known. In the adult respiratory distress syndrome [25] or ischemia-reperfusion syndromes [26] such as observed after liver transplantation [27] platelets are powerful and important mediators of tissue injury.

The pervasiveness of platelet sequestration in the critically ill hints that platelet sequestration may be a pathogenic process many organs.

**Theoretical advantages of ∆PC/∆t<sub>2→10</sub>**

One reason that ∆PC/∆t<sub>2→10</sub> may discriminate better than absolute PC is that inter-individual variation is reduced. Intra-individual variation in PC amounts is only 30% of the inter-individual variation in healthy persons [28,29].

Major methodological criteria which a physiologic measure used in a scoring system should fulfill are reproducibility, responsiveness and validity [30].

*Responsiveness* means that a measure detects clinically meaningful changes in the process of interest, and that changes in the measure correspond to clinically significant changes. With regard to this criterion it is contradictory to transform a responsive, continuous parameter into a discontinuous parameter with only a limited number of values. Moreover scoring systems such as SOFA (sequential organ failure score; [31]) or MODS (multiple organ dysfunction score; [30]) only start to score the PC as abnormal if it is subnormal. For example a PC>150 has 0 SOFA points, and will still have 0 points when the PC drops 250 on day 2 to 160 on day 10, a drop that we find is associated with increased mortality. Although the practical advantage is obvious, namely calculating a total score without a computer, important information is lost in this process. Yet, the SOFA-authors [31], like the MODS-authors [30] have subsequently observed that changes in their organ scores (i.e. ∆SOFA or ∆MODS) are also powerful predictors of outcome in addition to the initial scores themselves. The added value of ∆SOFA or ∆MODS is intuitively logical since these incremental increases in organ dysfunction portend by definition additional, more recent information. The special relevance of these incremental scores has been interpreted as reflecting de novo events that arise at the ICU, and may thus be amenable to therapeutic intervention. We believe that the same phenomenon is apparently true for ∆PC/∆t<sub>2→10</sub>.
Validity is the extent to which a parameter is a meaningful representation of the entire spectrum of the process of interest. Although the authors who incorporated PC into their scoring systems considered PC a useful and valid parameter, it is in fact unclear for which pathophysiological process it is valid. The SOFA authors call PC a "coagulation" parameter while MODS authors call it an "hematological" parameter. Coagulation and hematology are two rather broad and different processes. In fact it may turn out that PC and especially $\Delta PC/\Delta t$ reflect endothelial activation in many instances, as argued above. Thus we think that although PC and $\Delta PC/\Delta t$ are useful parameters, the process they reflected is not established.

Although it is obviously futile for application as a solitary parameter, we think $\Delta PC/\Delta t_{2\rightarrow10}$ could be considered for inclusion in future scoring systems.

Clinical and research implications

In clinical practice, $PC_{2}$ and $\Delta PC/\Delta t_{2\rightarrow10}$ are not difficult to assess, even without making a graph or performing calculations. Simple observation of the PC over a number of days will easily show whether it is decreasing, increasing or does not change after day 2. Our results illustrate that stable platelet counts, even in the so-called normal range (150-350 $\cdot 10^9$/l) are not ideal in many circumstances. In a patient who is recovering from severe injury the PC should be high-normal or supranormal after 1 week [10]. If the PC fails to rise in the first week, even if it is 200 $\cdot 10^9$/l, this should alert the clinician to potential complications.

If platelet sequestration is a pathogenic process and $\Delta PC/\Delta t_{2\rightarrow10}$ reflects platelet sequestration, this raises the logical question if inhibition of platelet sequestration will improve outcome. Analysis of intervention trial data with respect to $\Delta PC/\Delta t_{2\rightarrow10}$ may be useful for addressing this question. Like platelets, the agents protein C [32], antithrombin-III [33], glycoprotein IIb/IIIa (GPIIb/IIIa; [34]) and P-selectin [35] are all involved at intersection of the coagulatory and inflammatory processes. Thus these agents (i.e. activated protein C, antithrombin-III) or their inhibitors (i.e. GPIIb/IIIa-inhibitors or P-selectin inhibitors) are prime candidates for an examination of their impact on $\Delta PC/\Delta t_{2\rightarrow10}$.

In conclusion, serial platelet counts carry important information in critically ill patients. Taking the biphasic changes of PC into account helps to assess what is normal and what is abnormal. Scoring systems might be improved by accommodating the information contained in changes in platelet counts. Although some may take the process of platelet sequestration for granted, it is obvious that a fundamental process must be involved as it occurs in the large variety of critically ill patients. Intervention studies may show whether platelet sequestration is a process that is causal to mortality or whether it is only another of the many markers that have been associated with poor outcome in the ICU.

ACKNOWLEDGEMENT

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