

Thrombocytopenia in critically ill surgical patients: a case-control study evaluating attributable mortality and transfusion requirements

François Stephan, Jacques de Montblanc, Ali Cheffi and Francis Bonnet

Background: That thrombocytopenia results in increased mortality or transfusion requirements has not been confirmed by previous studies. We performed a case-control study in which 36 patients who developed severe thrombocytopenia of less than 50×10^9 platelets/l were carefully matched for the severity of underlying disease and other important variables.

Results: Seventeen (47%) thrombocytopenic patients died, versus 10 (28%) matched control patients who were not thrombocytopenic. Nine pairs had a discordant outcome, and in eight of these pairs the thrombocytopenic patient died (exact binomial probability 0.037). The estimated attributable mortality was 19.5% (95% confidence interval 3.2–35.8), and the estimated odds ratio was 2.7 (95% confidence interval 1.02–7.10). Thrombocytopenic patients had comparable values for severity of illness scores between day of admission and day of thrombocytopenia, in contrast with control patients who had a statistically significant decrease in severity of illness scores during the same period. Thirty (83%) of the thrombocytopenic patients required transfusion of blood products, versus 21 (58%) control patients (paired χ^2 test 4.92, $P < 0.04$). The estimated attributable transfusion requirement was 25% (95% confidence interval 5.4–44.6), and the estimated odds ratio was 1.52 (95% confidence interval 1.05–2.20).

Conclusion: The present study suggests that thrombocytopenia of less than 50×10^9 platelets/l may be a marker for more severe illness and increased risk of death, rather than causative, because a true causal relationship is not established. Thrombocytopenia also leads to an excess of blood product consumption.

Introduction

Thrombocytopenia is a well known complication in intensive care unit (ICU) patients. It has been associated with various risk factors, but mainly with sepsis [1–3]. The incidence of thrombocytopenia of less than 100×10^9 platelets/l in ICU patients has been reported to vary from 23 to 41%, but lower frequencies (10–17%) have been reported for counts lower than 50×10^9 platelets/l [1–3]. Mortality rates as high as 38–54% have been observed, and have been reported to be proportional to the nadir of the platelet count [1,3,4]. Previous studies have not clearly demonstrated that thrombocytopenia results in increased mortality or increased transfusion requirements, however. Two independent factors have made this important and seemingly straightforward issue difficult to resolve.

First, mortality rates are high in such patients for many reasons. Numerous studies [1,3,5–7] have demonstrated that severe underlying illness predisposes to the develop-

ment of thrombocytopenia in ICU patients, and the influence of thrombocytopenia on mortality is therefore difficult to assess. Although thrombocytopenia in the critically ill is more often a symptom than a disease process *per se*, it might increase mortality in several ways. Thrombocytopenia can result in a mild, moderate, or severe haemorrhagic disorder, which could enhance the risk of morbidity and mortality in critically ill surgical patients [8]. The adverse effects of anaemia in such patients have also recently been discussed [9,10]. Apart from its haemostatic effect, thrombocytopenia also increases the susceptibility to and severity of certain infections [11]. Although several studies have found a relationship between thrombocytopenia and the likelihood of death, especially in septic patients [1,3,4,7,12], thrombocytopenia has rarely been identified as an independent predictive factor of death using multiple logistic regression [5,6,13]. Nevertheless, these previous studies failed to reach any definite conclusions regarding whether thrombocytopenia *per se* was

Addresses: Service d'Anesthésie-Réanimation Chirurgicale. Hôpital Tenon, Paris, France

Correspondence: Dr François Stéphan, Service d'Anesthésie-Réanimation, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France.
Tel: +33 (1) 49 81 23 83;
fax: +33 1 49 81 23 80;
e-mail: francois.stephan@hmn.ap-hop-paris.fr

Keywords: APACHE II score, bleeding, case-control study, intensive care unit, mortality, prognosis, sepsis, transfusion, thrombocytopenia, underlying disease

Received: 6 July 1999
Revisions requested: 31 August 1999
Revisions received: 20 September 1999
Accepted: 24 September 1999
Published: 25 October 1999

Crit Care 1999, 3:151–158

The original version of this paper is the electronic version which can be seen on the Internet (<http://ccforum.com>). The electronic version may contain additional information to that appearing in the paper version.

© Current Science Ltd
Print ISSN 1364-8535 Online ISSN 1466-609X

responsible for the poorer prognosis, or whether this higher mortality simply reflected more severe underlying illness.

Second, the threshold value for severe thrombocytopenia that is supposed to jeopardize the prognosis is difficult to determine. We and others [1,3,13] have suggested that a platelet count less than $50 \times 10^9/l$ is associated with a poor outcome. Moreover, guidelines for platelet transfusion [8] have proposed that the threshold value of 50×10^9 platelets/l is indicative of platelet transfusion requirement in surgical patients.

One of the commonest methods to evaluate excess mortality is to perform a case-control study in which confounding variables (eg severity of underlying illness, reason for hospitalization, and so forth) are carefully matched in the two populations. To date, however, no case-control studies that have evaluated morbidity and mortality associated with thrombocytopenia in ICU patients have been published in which these important variables have been carefully matched.

We therefore designed a case-control study to determine to what extent severe thrombocytopenia (defined as $<50 \times 10^9$ platelets/l) increases mortality and blood product requirements in surgical ICU patients.

Methods

Study design

We performed a matched cohort study, with a matched control patient without thrombocytopenia for each thrombocytopenic patient (1:1 matching). The study was conducted in the Service de Réanimation Chirurgicale of Tenon University Hospital in Paris. This 8-bed ICU admits patients from all surgical departments and operating rooms of the hospital. The study period ran from January 1, 1996 to December 31, 1996, during which time 298 patients were admitted to the ICU and thrombocytopenic patients were prospectively identified.

Case identification

Platelet count was performed daily for all patients. Patients who experienced even a single episode of thrombocytopenia of less than 50×10^9 platelets/l during the ICU stay were classified as 'cases'. Low platelet counts were confirmed by direct examination of the blood smear. Platelet transfusions were administered to actively bleeding patients and patients scheduled for emergency surgery if their platelet count fell below $50 \times 10^9/l$. Likewise, platelet transfusions were administered to patients at risk for bleeding complications (eg postoperative patients, or after gastrointestinal bleeding) when their platelet count fell below $20 \times 10^9/l$ [8,14].

None of patients with a history of platelet disorders, haematologic malignancies or chemotherapy, splenec-

tomy, mechanical heart valves, or patients undergoing cardiopulmonary bypass surgery were included in the patient population.

Matching and selection of control patients

Control patients had to have had no evidence of severe thrombocytopenia ($<50 \times 10^9$ platelets/l) at any time during hospitalization in the ICU. A computer-generated list of eligible control patients was obtained from a database that included 695 patients hospitalized between November, 1995 and March, 1998. Control patients were selected according to the following matching criteria: age (± 5 years), Acute Physiology and Chronic Health Evaluation (APACHE) II score calculated on the first day of ICU admission (± 5 points), primary diagnosis and duration of stay in the ICU (± 5 days). The list of potential control patients was reviewed for the best possible match, giving highest priority to primary diagnosis, duration of stay in the ICU, APACHE II score and age. In the case of multiple acceptable control patients, the one with the date of ICU admission closest to that of the patient was chosen.

Collection of data

The following information was recorded: primary diagnosis; age; sex; dates of admission and discharge from the ICU; previous health status; severity of underlying medical conditions stratified according to the criteria of McCabe and Jackson [15] as fatal, ultimately fatal and nonfatal; first-day organ dysfunction and/or infection (ODIN) score [16], based on the presence or absence of cardiac, respiratory, renal, hepatic, neurologic, haematologic dysfunctions and/or infection; red blood cells (RBCs); fresh frozen plasma and platelet transfusion requirements; and full blood count and coagulation studies (factor V assay and D-dimer detection were performed only when prothrombin time was abnormal). The severity of illness was evaluated with the first-day APACHE II score [17] and the first-day new Simplified Acute Physiology Score (SAPS) II [18].

The criteria of sepsis have previously been reported [19]. Shock was defined as a decrease in systolic blood pressure (<90 mmHg) despite adequate vascular filling or the need for vasoactive drugs (dopamine $>5 \mu\text{g/kg}$ per min, dobutamine, epinephrine, or norepinephrine).

The definition of disseminated intravascular coagulation (DIC) required the following four criteria: a platelet count less than $150 \times 10^9/l$; a decrease in prothrombin level activity to less than 50%; a decrease in the level of factor V to less than 50%; and the presence of fibrin degradation products (D-dimers).

Statistical analysis

Analysis of prior data from our unit indicated that the odds ratio for death was 3.9 for cases and that the mortality rate

for control patients was 23% [3]. On the basis of these results, we estimated that 28 patients in each group (control and case) would be required to test the null hypothesis at the 0.05 significance level with a power of 0.7 [20].

The attributable mortality due to severe thrombocytopenia was defined as the crude mortality rate of the control patients subtracted from that of the cases. The point estimate of the attributable mortality and 95% confidence intervals (CIs) were calculated as previously described [21]. McNemar's test with continuity correction and exact binomial probabilities were used to determine whether the crude mortality rates of the cases and control patients were significantly different [21]. Because the study involved a matched cohort, the odds ratio was used as a measure of relative risk. Because incidence of outcome is more than 10%, correction of the odds ratio was made according to the method of Zhang and Yu [22] in order to represent better the true relative risk. The 95% CI of the odds ratio was calculated using Miettinen's test-based approach [21].

Differences in medians were tested using Wilcoxon's test for continuous variables and the χ^2 test for categorical variables, with Yates' correction when appropriate. Quantitative data were expressed as means \pm standard deviation. $P < 0.05$ was considered statistically significant.

Results

Study population

During the study period, 36 of the 298 studied ICU patients developed severe thrombocytopenia of less than 50×10^9 platelets/l, producing a global incidence rate of 12 episodes of thrombocytopenia per 100 admissions. Thrombocytopenia occurred 3.2 ± 4.8 days (median 2 days, interquartile range 2.5 days, range 0–26 days) after ICU admission, for a mean duration of 3.4 ± 2.9 days (median 2 days, interquartile range 4 days, range 1–13 days). Thrombocytopenia was related to sepsis in eight patients; sepsis and DIC in 11 patients; bleeding in nine patients; bleeding and DIC in six patients; undetermined shock and DIC in one patient; and haemolysis–elevated liver enzymes–low platelets syndrome with DIC in one patient. Matching was performed for these 36 patients.

On admission to ICU, the mean platelet count was $127 \pm 75 \times 10^9/l$ (median 116) versus $199 \pm 123 \times 10^9/l$ (median 161) in cases and control patients, respectively (not significant). During ICU stay, mean nadir platelet count was $28 \pm 14 \times 10^9/l$ (median 29.5) versus $184 \pm 142 \times 10^9/l$ (median 114); mean nadir haemoglobin value was 6.9 ± 1.7 g/dl (median 7.2) versus 8.7 ± 2.3 g/dl (median 8; $P = 0.009$); and mean nadir leucocyte count was $6.2 \pm 4.1 \times 10^9/l$ versus $10.2 \pm 4.9 \times 10^9/l$ ($P < 0.0004$) in cases and control patients, respectively. Nineteen cases (52.7%) and eight control patients (22.2%) had evidence of DIC ($P < 0.01$).

Table 1

Results of matching of cases to control patients using four major criteria

Criterion	Proportion of cases matched to control patients	
	<i>n/n</i>	%
Same primary diagnosis	35/36	97
Same duration of stay in ICU (± 5 days)	31/36	86
Same APACHE II score (± 5)	29/36	81
Same age (± 5 years)	27/36	75

APACHE, Acute Physiology and Chronic Health Evaluation; ICA, intensive care unit.

Closeness of matching

The median age of the cases was 65 years (range 27–104 years, mean 60.7 years) versus 65 years (range 27–83 years, mean 60.6 years) for control patients. Twenty-one (58%) case–control pairs differed by no more than 3 years, and 27 (75%) by no more than 5 years (Table 1). The median APACHE II score of cases was 21 (range 5–41, mean 20.8) versus 21 for control patients (range 4–37, mean 22.7). The median duration of ICU stay of cases was 5 days (range 1–35 days, mean 8.3 days) versus 4 days for control patients (range 1–26 days, mean 6.4 days). Thirty-five (97%) of the pairs were matched for primary diagnosis. Overall, matching was successful for 243 out of 288 (84.3%) variables.

Because the study end point — mortality — is strongly related to severity of illness and/or initial respiratory status [17,18], we controlled matching by comparing another seven criteria that evaluated the severity of disease in the two groups of patients (Table 2). No significant differences in these indices were observed between cases and control patients. This was particularly the case when comparing the four variables that were individually predictive of survival for all patients: mean SAPS II score, mean number of organ-system failures, number of patients with cardiac failure on admission, and number of patients with renal failure on admission. The sex ratio of the two groups was also similar. Finally, the dates of admission of cases and control patients differed by less than 1 year in 27 pairs (75%).

Mortality

Seventeen (47%) cases died, versus 10 (28%) control patients (Table 3). Twenty-seven matched pairs had a concordant outcome (18 lived and nine died). Nine pairs had a discordant outcome, and in eight of these pairs the case died (exact binomial probabilities: 0.037). The estimated attributable mortality was 19.5% (95% CI 3.2–35.8), and the estimated odds ratio was 2.7 (95% CI 1.02–7.10).

Table 2**Matching criteria and clinical characteristics of the study population**

Parameter	Cases (n = 36)	Control patients (n = 36)	P
Matching criteria			
Primary diagnosis			0.99
Septic shock [n (%)]	12 (33)	12 (33)	
Postoperative bleeding, gastrointestinal hemorrhage, trauma [n (%)]	14 (39)	13 (36)	
Acute respiratory failure [n (%)]	3 (8)	3 (8)	
Complication during post partum [n (%)]	2 (6)	2 (6)	
Cardiac failure [n (%)]	1 (3)	2 (6)	
Miscellaneous [n (%)]*	4 (11)	4 (11)	
Duration of stay in ICU (days)	8.3 ± 8.4	6.5 ± 6.4	0.29
APACHE II score (points)	22.7 ± 8.6	20.9 ± 8.3	0.35
Age (years)	60.7 ± 19.1	60.6 ± 17.4	0.97
Characteristics			
Sex (male/female)	20/16	22/14	0.63
Severity of underlying disease			0.81
Fatal or ultimately fatal [n (%)]	19 (53)	18 (50)	
Nonfatal [n (%)]	17 (47)	18 (50)	
Previous health status			0.80
No functional or moderate limitation [n (%)]	25 (69)	26 (72)	
Serious limitation or bedridden or institutionalized [n (%)]	11 (31)	10 (28)	
SAPS II score (points)	49.7 ± 18.9	46.7 ± 21.9	0.54
Expected mortality (%) [†]	46.0	39.1	–
ODIN model on admission			–
Cardiac failure [n (%)]	22 (61)	21 (58)	
Respiratory failure [n (%)]	30 (83)	30 (83)	
Haematologic failure [n (%)]	20 (55)	13 (36)	
Neurologic failure [n (%)]	6 (17)	10 (28)	
Hepatic failure [n (%)]	1 (3)	2 (5)	
Presence of infection [n (%)]	19 (53)	16 (44)	
Total no. of organ system failure	2.8 ± 1.2	2.9 ± 1.2	0.60

*Miscellaneous included two cases of nosocomial pneumonia, one case of acute pancreatitis, and one case of undetermined shock.

[†]Calculated from the equation proposed by Le Gall *et al.* [18].

APACHE, Acute Physiology and Chronic Health Evaluation; ODIN, organ dysfunction and/or infection; ICU, intensive care unit; SAP, Simplified Acute Physiology Score.

Primary diagnosis in the nine discordant case–control pairs was septic shock in six pairs, acute pancreatitis in one pair, undetermined shock in one pair and haemorrhagic shock in one pair. Causes of mortalities included refractory septic shock in eight cases (47%) and four control patients (40%); multiple organ failure-related sepsis in five cases (29%) and three control patients (30%); uncontrolled bleeding in four cases (24%) and two control patients (20%); and one undetermined shock in one control (10%).

Sensitivity analyses were done to explore whether mortality risk varies according to exposure. Thus, 17 cases experienced a thrombocytopenia below 50×10^9 platelets/l for more than 3 days. Mortality rate was 47%,

Table 3**Crude mortality, attributable mortality, and odds ratio of death due to severe thrombocytopenia in intensive care unit patients**

Variable	Point estimate		
	n/n	%	95% CI
Crude mortality (cases)	17/36	47.2	
Crude mortality (control patients)	10/36	27.8	
Attributable mortality	7/36	19.4	3.2–35.8
Odds ratio		2.7	1.02–7.10

CI, confidence interval.

Table 4**Comparison of illness severity scores between cases and control patients on the day of admission and on the day of onset of thrombocytopenia in the nine discordant pairs**

Score	Cases (<i>n</i> = 9)	Control patients (<i>n</i> = 9)	P
APACHE II (median)			
Day of admission	25.2 ± 4.2 (25)	24.0 ± 6.7 (26)	NS
Day of thrombocytopenia	30.7 ± 8.3 (47)	12.9 ± 5.2 (11)*	0.04
SAPS II (median)			
Day of admission	46.6 ± 10.5 (47)	46.9 ± 16.9 (40)	NS
Day of thrombocytopenia	58 ± 18.2 (51)	32.1 ± 10.4 (31)*	0.04
ODIN model (median)			
Day of admission	3.3 ± 1.4 (4)	3.0 ± 1.0 (3)	NS
Day of thrombocytopenia	3.8 ± 0.67	0.7 ± 1 (0)*	0.008
Expected mortality (%) [†]			
Day of admission	39.1	39.1	–
Day of thrombocytopenia	64.0	12.8	–

**P* < 0.05 by Wilcoxon's signed-rank test (score on day of admission versus score on day of thrombocytopenia in control group).

[†]Calculated from the equation proposed by Le Gall *et al.* [18].

versus 53 in patients without a prolonged thrombocytopenia (not significant). Likewise, among the 16 cases transfused with platelets, eight died (50%) compared with nine (45%) cases who were not transfused (not significant). A last sensitivity analysis was done on the timing variable. In 15 cases, thrombocytopenia occurred more than 2 days after ICU admission. Mortality rate was 65% in these patients compared with 35% in cases in whom thrombocytopenia occurred 2 days or less after ICU admission (*P* = 0.008).

Two time-point analyses of illness severity scores in the nine discordant pairs showed that the APACHE II, SAPS II and ODIN model scores were significantly higher for cases than for control patients on the day of thrombocytopenia (Table 4). Moreover, cases had comparable values of severity of illness scores between day of admission and day of thrombocytopenia; this was contrary to the situation with control patients, who had a statistically significant decrease in severity of illness scores during the same period (Table 4).

Blood product consumption

Thirty (83%) cases required transfusion of blood products, versus 21 (58%) control patients (Table 5). Thirteen pairs had discordant transfusion requirements, and in 11 of these pairs the cases were transfused (paired χ^2 4.92, *P* < 0.04). The estimated attributable transfusion requirement was 25% (95% CI 5.4–44.6), and the estimated odds ratio was 1.52 (95% CI 1.05–2.20).

Table 5**Crude transfusion requirements, attributable transfusion requirements, and odds ratio of transfusion requirements due to severe thrombocytopenia in intensive care unit patients**

Variable	Point estimate		
	<i>n/n</i>	%	95% CI
Crude transfusion requirements			
Cases	30/36	83.0	
Control patients	21/36	58.0	
Attributable transfusion requirements	9/36	25.0	5.4–44.6
Odds ratio		1.52	1.05–2.20

CI, confidence interval.

Units of RBCs transfused were 8.0 ± 7.0 (median 7.5) versus 2.6 ± 4.3 (median 1.5; *P* < 0.0001), and units of fresh frozen plasma transfused were 5.0 ± 7.0 (median 1.0) versus 1.0 ± 2.0 (median 0; *P* = 0.05) in cases and control patients, respectively. Sixteen cases (44.4%) received platelet transfusion (5.3 ± 7.7 units of platelets transfused), versus no control patients. In eight patients (one died), platelet transfusions resulted in a rise of platelet count to greater than 50 × 10⁹/l, with a correction of thrombocytopenia a few days later. In eight patients (seven died), only a transient rise of platelet count was noted and thrombocytopenia persisted during the entire ICU stay, despite platelet transfusion. After onset of thrombocytopenia,

4.4±7.2 units of RBCs and 2.5±5.4 units of fresh frozen plasma were transfused. This represents about 50% of the total transfusion requirements.

Discussion

The present results suggest that thrombocytopenia of less than 50×10^9 platelets/l in ICU patients is associated with increased mortality, with a relative risk of 2.7 (95%CI 1.02–7.10), and with excess blood product consumption, with a relative risk of 1.52 (95%CI 1.05–2.20).

The incidence rate of thrombocytopenia reported in the present study (12% surgical ICU patients) is in the range reported in previous studies [1,3]. There are many explanations for the thrombocytopenia observed in the context of infection. DIC [23], immune mechanisms [23], and haemophagocytic histiocytes [24,25] are the commonest mechanisms of increased platelet destruction during bacterial infection. In critically ill surgical patients, blood loss with subsequent volume replacement using crystalloids or colloids, when sufficiently severe, can significantly decrease the platelet count [26]. Likewise, a fall in platelet count has been noted after blood transfusions, and the incidence of thrombocytopenia has been specifically reported to be directly proportional to the number of RBC transfusions [2].

Patients with more severe underlying illness are more likely to develop thrombocytopenia [1–3,5–7], and the severity of underlying illness has an important impact on the outcome of ICU patients with severe thrombocytopenia [1,3,5–7]. As previously suggested, mortality appears to be proportional to the nadir platelet count [1,3,4]. Relatively old studies [7,12,27] reported that thrombocytopenia was associated with an increased mortality rate in septic patients. Recent studies using multivariate analysis have reported conflicting results, however. Sprung *et al* [5], in a large prospective study, identified thrombocytopenia ($<100 \times 10^9$ platelets/l) as an independent predictor of poor prognosis in septic patients, corresponding to a relative risk of death of 1.66 (95%CI 1.06–2.60). In a recent multicenter prospective study, Brun-Buisson *et al* [13] also reported a relative risk of late mortality of 1.5 (95% CI 1.2–2.0) in severely ill septic thrombocytopenic patients (platelet count $<50 \times 10^9$ /l). Another smaller study [6] showed comparable results in septic patients. On the other hand, Pittet *et al* [28] did not identify thrombocytopenia as an independent predictor of mortality at the onset of sepsis in ICU patients, like Brun-Buisson *et al* [13] did for early mortality. Finally, when the entire cohort of ICU patients was studied, thrombocytopenia was not identified as a variable that was independently associated with death in two studies [3,6]. These discrepancies may be attributable to differences in the variables and analytical methods used, and could also result from the complex interactions noted in multivariate analysis.

Case–control studies require a considerably smaller sample size than the corresponding longitudinal studies, and is as effective as the cohort study as a basis for causal inference [29]. Critical to the validity of this study is the success in matching cases and control patients for important confounding variables, especially the severity of underlying illness. We used three variables that are strongly correlated with outcome in patients admitted to ICUs to match cases and control patients [17,18]: age, a severity of disease scoring system (APACHE II), and specific diagnostic categories according to the one main reason for admission. Matching was 84.3% successful for 288 possible variables. To verify the adequacy of matching for severity of underlying illness and primary diagnosis independently, we compared the cases and control patients with respect to another seven potentially confounding variables. No statistically significant differences in these indices were observed between cases and control patients. It may be argued that we matched patients at the time of admission. We realize that this does not reflect the severity of illness at the time of thrombocytopenia, and that matching on variables recorded at the time or just before the diagnosis of thrombocytopenia may have yielded different results. The reliability of systems such as APACHE II, SAPS II and ODIN is not sufficiently defined to study the daily probability of death, however. Moreover, thrombocytopenia is linked to admission characteristics and/or diagnosis, because nearly 60% of patients with thrombocytopenia occurred during the first 2 days after ICU admission.

We found that severe thrombocytopenia is associated with increased mortality, mainly in septic patients, thereby confirming the results of previous cohort studies [5,6,13]. In the ICU setting, however, thrombocytopenia is a symptom that has been associated with several acute diseases [1–3,23–26]. It is therefore difficult to distinguish causes from consequences of severe thrombocytopenia clearly in critically ill patients. For example, it is difficult to state that bleeding not represent the results of thrombocytopenia rather than the cause. Although matched case–control studies are attractive because matching assumes comparability for certain variables, the finding of a higher mortality in cases compared with in control patients only implies an association between mortality and thrombocytopenia. Thus, the present analysis identified an increased difference in severity of illness scores between cases and control patients between the day of admission and the day of thrombocytopenia. The finding that illness severity decreased over time in control patients, but remained constant in the cases, supports the notion that severe thrombocytopenia probably largely reflects the unfavourable course of the underlying disease and possibly the aggravating role of thrombocytopenia itself. Thrombocytopenia lasting for less than 3 days confers a similar risk to that of thrombocytopenia for many

days. As the present results show, platelet transfusion failed to restore a normal platelet count, but normalization of platelet count, when it occurred, was associated with better prognosis, as previously reported [3,24,27].

Patients who require intensive platelet support frequently have complex medical problems, including DIC, clinical bleeding and uncontrolled sepsis. Patients in this setting receive multiple drugs and frequent blood product transfusions. Patients with thrombocytopenia secondary to sepsis often require platelet transfusions, although their response is often suboptimal because of continued platelet destruction, reflecting the persistence of the underlying disease. Likewise, in patients receiving massive transfusion, thrombocytopenia is due both to consumption of platelets and to dilution by transfused blood and colloid fluid resuscitation. These patients may also have platelet function defects due to DIC, hypothermia and 'stunned' recently transfused platelets. Patients may remain mildly thrombocytopenic for several days before having a rebound thrombocytosis [30]. Of interest, the mortality impact of thrombocytopenia occurred during the first 2 days after ICU admission, which is quite different from late-onset ICU-acquired thrombocytopenia. This result is in agreement with a previous analysis [13] that indicated that late mortality is essentially associated with the characteristics of the underlying disease.

The mechanism of increased mortality directly related to thrombocytopenia is difficult to assess, but several points should be considered. First, the present results show that severely thrombocytopenic patients required more blood product transfusions. In addition to the possible volume overload, higher postoperative infection rates have been reported in patients who received blood transfusions [31]. Another study [32], however, did not confirm this relationship. Second, platelets play key and multifactorial roles in antimicrobial host defences [11]. For example, in the absence of neutropenia, thrombocytopenia has been positively correlated with an increased incidence and severity of pneumonia in elderly patients [33]. Third, cases had a lower nadir haemoglobin value than control patients. Two recent studies have [9,10] shown that patients with a cardiovascular diagnosis and a high degree of acute illness appear to be at increased risk of death from a moderate degree of anaemia. Finally, severe thrombocytopenia is an important risk factor for spontaneous intracerebral haemorrhage associated with a high mortality in critically ill patients [34].

Conclusion

The present report shows that thrombocytopenia of less than 50×10^9 platelets/l is associated with excess mortality that is independent of the patient's age and initial severity of illness, and leads to excess blood product consumption, thus imposing a significant economic burden. Thrombo-

cytopenia appears to be mostly a marker of severity of underlying processes, rather than causally related to death. Thus, the exact relationship between thrombocytopenia and mortality has yet to be elucidated, especially in septic patients. Further studies of the specific role of thrombocytopenia in shock and infections are necessary. Moreover, the risks and benefits of the various strategies for the management of thrombocytopenic ICU patients should be re-evaluated in a variety of clinical settings.

Acknowledgments

The authors thank Prof Jean-Yves Fagon for his critical review of the manuscript.

References

- Baughman RP, Lower EE, Flessa HC, Tollerud DJ: **Thrombocytopenia in the intensive care unit.** *Chest* 1993, **104**:1243–1247.
- Hanes SD, Quarles DA, Boucher BA: **Incidence and risk factors of thrombocytopenia in critically ill trauma patients.** *Ann Pharmacother* 1997, **31**:285–289.
- Stéphan F, Hollande J, Richard O, *et al*: **Thrombocytopenia in a surgical intensive care unit: incidence, risk factors and outcome.** *Chest* 1999, **115**:1363–1370.
- Marshall JC, Cook DJ, Christou NV, *et al*: **Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome.** *Crit Care Med* 1995, **23**:1638–1652.
- Sprung CL, Peduzzi PN, Shatney CH, *et al*: **Impact of encephalopathy on mortality in the sepsis syndrome.** *Crit Care Med* 1990, **18**:801–806.
- Lee KH, Hui KP, Tan WC: **Thrombocytopenia in sepsis: a predictor of mortality in the intensive care unit.** *Singapore Med J* 1993, **34**:245–246.
- Kreger BE, Craven DE, McCabe WR: **Gram-negative bacteria. Re-evaluation of clinical features and treatment in 612 patients.** *Am J Med* 1980, **68**:344–355.
- Practice guidelines for blood component therapy. A report by the American Society of Anesthesiologists task force on blood component therapy.** *Anesthesiology* 1996, **84**:732–747.
- Carson JL, Duff A, Poses RM, *et al*: **Effect of anemia and cardiovascular disease on surgical mortality and morbidity.** *Lancet* 1996, **348**:1055–1060.
- Hébert PC, Wells G, Tweeddale M, *et al*: **Does transfusion practice affect mortality in critically ill patients?** *Am J Respir Crit Care Med* 1997, **155**:1618–1623.
- Yeaman MR: **The role of platelets in antimicrobial host defense.** *Clin Infect Dis* 1997, **25**:951–970.
- Svanbom M: **A prospective study on septicemia. Clinical manifestations and complications, results of antimicrobial treatment and report of a follow-up study.** *Scand J Infect Dis* 1980, **12**:189–206.
- Brun-Buisson C, Doyon F, Carlet J, *et al*: **Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units.** *JAMA* 1995, **274**:968–974.
- Kitchens CS: **Disseminated intravascular coagulation.** *Curr Opin Hematol* 1995, **2**:402–406.
- McCabe WR, Jackson GC: **Gram-negative bacteria. I. Etiology and ecology.** *Arch Intern Med* 1962, **110**:847–855.
- Fagon J-Y, Chastre J, Novara A, Medioni P, Gibert C: **Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model.** *Intens Care Med* 1993, **19**:137–144.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system.** *Crit Care Med* 1985, **13**:818–829.
- Le Gall J-R, Lemeshow S, Saulnier F: **A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study.** *JAMA* 1993, **270**:2957–2963.
- American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee: **Definitions for sepsis and organ failures and guidelines for the use of innovative therapies in sepsis.** *Crit Care Med* 1992, **20**:864–874.

20. Townsend TR: **New aspects of case-control studies and clinical trials.** In: *Prevention and Control of Nosocomial Infections*. Edited by Wenzel RP. Baltimore: Williams and Wilkins; 1987:578–590.
21. Kirkwood BR: *Essential of Medical Statistics*. Cambridge, MA: Blackwell Scientific Publications; 1988.
22. Zhang J, Yu KF: **What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes.** *JAMA* 1998, **280**:1690–1691.
23. Wilson JJ, Neame PB, Kelton JG: **Infection-induced thrombocytopenia.** *Semin Thromb Hemostas* 1982, **8**:217–233.
24. François B, Trimoreau F, Vignon P, *et al*: **Thrombocytopenia in the sepsis syndrome: role of hemophagocytosis and macrophage colony-stimulating factor.** *Am J Med* 1997, **103**:114–120.
25. Stéphane F, Thiolière B, Verdy E, Tulliez M: **Role of hemophagocytic histiocytosis in the etiology of thrombocytopenia in patients with sepsis syndrome or septic shock.** *Clin Infect Dis* 1997, **25**: 1159–1164.
26. Spiess BD: **Hemorrhagic problems during the immediate post-operative period.** In: *Post anesthesia Care*. Edited by Vender JS, Spiess BD. Philadelphia: WB Saunders; 1992:131–140.
27. Oppenheimer L, Hryniuk WM, Bishop AJ: **Thrombocytopenia in severe bacterial infections.** *J Surg Res* 1976, **20**:211–214.
28. Pittet D, Thiévent B, Wenzel RP, *et al*: **Bedside prediction of mortality from bacteremic sepsis. A dynamic analysis of ICU patients.** *Am J Respir Crit Care Med* 1996, **153**:684–693.
29. Austin H, Hill HA, Flanders D, Greenberg RS: **Limitations in the application of case-control methodology.** *Epidemiol Rev* 1994, **16**: 65–76.
30. Schroeder ML: **Principles and practice of transfusion medicine.** In: *Wintrobe's Clinical Hematology*. Edited by Lee GR, Foerster J, Lukens J, *et al*. Baltimore: Williams and Wilkin; 1998:817–874.
31. Edna TH, Bjerkeset T: **Association between blood transfusion and infection in injured patients.** *J Trauma* 1992, **33**:659–661.
32. Vamvakas EC, Moore SB, Cabanela M: **Blood transfusion and septic complications after hip replacement surgery.** *Transfusion* 1995, **35**: 150–156.
33. Feldman C, Kallenbach JM, Levy H, *et al*: **Comparison of bacteremic community-acquired lobar pneumonia due to *Streptococcus pneumoniae* and *Klebsiella pneumoniae* in an intensive care unit.** *Respiration* 1991, **58**:265–270.
34. Oppenheim-Eden A, Glantz L, Eidelman LA, Sprung CL: **Spontaneous intracerebral hemorrhage in critically ill patients: incidence over six years and associated factors.** *Intens Care Med* 1999, **25**: 63–67.