Assessment of thrombocytopenia in critically ill patients

Mohammad A. Faramawy[a], Iman H. Galal[a], Asmaa M. Elasser[b]

Background Thrombocytopenia is commonly observed among critically ill patients.

Aim The aim of this study was to evaluate the incidence, risk factors, and the outcome of thrombocytopenia in patients admitted to the respiratory intensive care unit (RICU).

Materials and methods Data were collected from 50 adult patients admitted to the RICU in a 6-month period. The baseline platelet count was measured and was repeated every other day during the RICU stay period. Thrombocytopenia was defined as platelet count of less than $150 \times 10^9/l$.

Results The incidence of thrombocytopenia was 20% (10 patients). The overall mortality was 16%, of which 50% of the patients were having thrombocytopenia. The thrombocytopenic group had a higher mortality (40 vs. 10%, $P < 0.05$), a lower admission platelet count (215.3 ± 85.6 vs. 252.8 ± 73.2, $P < 0.05$), a lower nadir platelet count (111.1 ± 22.6 vs. 213.9 ± 53.2, $P < 0.001$), an increased transfusion requirement (30 vs. 2.5%, $P < 0.05$), and increased septic shock (40 vs. 2.5%, $P < 0.05$) compared with the nonthrombocytopenic group. Comorbidities, indications for RICU admission, the length of RICU stay, mechanical ventilation, days on mechanical ventilation, admission severity scores, bleeding, ICU-related complications, and medications administrated during the RICU stay did not differ significantly. A prolonged RICU stay of more than 15 days carried a 4.7 times higher incidence of development of thrombocytopenia. Thrombocytopenia differed significantly between survivors and nonsurvivors ($P < 0.05$), with a significant effect on mortality ($P = 0.034$).

Conclusion Thrombocytopenia is common among critically ill patients and affects the mortality significantly. Prolonged ICU stay and septic shock are among the risk factors for thrombocytopenia. *Egypt J Broncho* 8:143–148
© 2014 Egyptian Journal of Bronchology.

Introduction

Thrombocytopenia is defined as a platelet count of less than $150 \times 10^9/l$ [1–5]. The various comorbidities in the severely ill patient affect platelet homeostasis, and consequently, thrombocytopenia is very common in critically ill patients treated in the ICU. Furthermore, thrombocytopenia in critically ill patients is associated with an increased duration of hospital stay and increased mortality [3,4,6–9].

This study aimed at evaluating the incidence, risk factors, and the outcome of thrombocytopenia in patients admitted to the respiratory intensive care unit (RICU).

Materials and methods

This prospective observational study was conducted on all adult patients admitted to the RICU of both Ain Shams University Hospital and Abbassia Chest Hospital more than 72 h in the period between January 2012 and July 2012. For all patients, demographic data, comorbidities, detailed medical history taking (from the patients or relatives), thorough clinical examination, routine laboratory investigation, plain chest radiography, baseline arterial blood gases analysis, primary diagnosis, and the cause of admission to the RICU were documented. Recording of complications and interventions during the RICU stay were performed for all patients including the duration of RICU stay, mechanical ventilation (MV), days of MV, bleeding, and the need for blood transfusion. The severity of illness was evaluated with first-day scores including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [10], the Sequential Organ Failure Assessment (SOFA) score [11], Simplified Acute Physiology Scores II (SAPS II) [12], and the Multiple Organ Dysfunction Score (MODS) [13]. For all patients, estimation of the first-day baseline platelet count was performed and was repeated every other day during the whole period of RICU stay using Horiba ABX micros 60, Sysmex, and Medonic (San Diego, USA), with identification of the day of occurrence of thrombocytopenia±the day of occurrence of bleeding, and the day of blood or platelet transfusion. A normal platelet count was regarded as platelet count of at least $150 \times 10^9/l$. Thrombocytopenia was defined as platelet count of less than $150 \times 10^9/l$ [1–5]. The nadir platelet count refers to the lowest platelet count recorded during the RICU stay. Patients were divided into two groups: the thrombocytopenia group with a platelet count of less than $150 \times 10^9/l$ at any time during

their RICU stay and the nonthrombocytopenia group with a platelet count of at least $150 \times 10^9/l$. Exclusion criteria included patients with thrombocytopenia on admission, a history of platelet disorders, hematological malignancies, splenectomy, recent radiotherapy and/or chemotherapy, or patients on bone marrow-platelet suppressive agents. The study was approved by the institutional ethics committee.

Statistical analysis

Parametric numerical data were expressed as mean ± SD, whereas nonparametric numerical data were expressed as median, interquartile range, frequency, and percentage. The Student t-test was used to assess the statistical significance of the difference between two study group means. The Mann–Whitney U-test was used to assess the statistical difference of nonparametric variables between two study groups. The χ^2-test was applied to examine the relationship between two qualitative variables. The Fisher exact test was used to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of cells. Logistic regression was applied to predict the presence or the absence of an outcome on the basis of a set of independent variables. Statistical significance was set at P value less than 0.05. Statistical analyses were performed utilizing the Statistical Package for Social Sciences software (SPSS for Windows, version 15.0; SPSS Inc., Chicago, Illinois, USA).

Results

During the 6-month study period, 50 patients were admitted to the RICU. Table 1 shows the baseline characteristics and the outcome of all included patients. The mean ± SD age was 54.3 ± 14.7 years, with a range of 25–86 years: 29 (58%) patients were male and 21 (42%) were female. The major indication for RICU admission was respiratory failure (32 cases). Patients had a median first-day APACHE II score of 20, a median first-day SOFA score of 4, a median first-day SAPS II of 40, and a median first-day MODS of 5. The median duration of RICU stay was 7 days; 31 cases were mechanically ventilated with 5 days' median duration of MV. RICU mortality was 16%, of which 50% of the cases were thrombocytopenic. Thrombocytopenia developed in 10 (20%) patients. A total of six patients (12% of the study population) experienced a bleeding event, four of which were among patients with thrombocytopenia. Other ICU-related complications included septic shock in five patients, acute respiratory distress syndrome in three patients, and ventilator-associated pneumonia in one patient. Blood transfusion was required in

Table 1 Baseline characteristics and outcomes of all patients

Variables	Values
Age[a] (years)	54.3 ± 14.7 (53.5)
Sex (M/F) [n (%)]	29/21 (58/42)
Admission APACHE II[a]	20.2 ± 9.6 (20)
Admission SOFA[a]	5.2 ± 4.3 (4)
Admission SAPS II[a]	40.1 ± 13 (40)
Admission MODS II[a]	5.9 ± 3.1 (5)
Days in RICU[a]	11.7 ± 12.8 (7)
Days in RICU [n (%)] (days)	
≤15	38 (76)
>15	12 (24)
MV [n (%)]	31 (62)
Days on MV[a]	11.3 ± 15.1 (5)
Hemoglobin[a]	12.7 ± 2.6 (13)
Total leukocytic count[a]	12.3 ± 6 (12)
Co-morbidity [n (%)]	
No	9 (18)
Cardiac	33 (66)
Diabetes	19 (38)
Hepatic	5 (10)
Indication for RICU admission [n (%)]	
Respiratory failure	32 (64)
Sepsis	7 (14)
Lung mass	1 (2)
Pleural disease	4 (8)
Pulmonary embolism	2 (4)
Cardiac disease	4 (8)
Use of drug-induced thrombocytopenia [n (%)]	
UFH + others	14 (28)
LMWH + others	11 (22)
Others	25 (50)
Thrombocytopenia [n (%)]	10 (20)
Platelet count on admission	245 ± 76.4
Nadir platelet count	193 ± 63.8
Blood transfusion [n (%)]	4 (8)
Complications [n (%)]	
Bleeding	6 (12)
VAP	1 (2)
ARDS	3 (6)
Septic shock	5 (10)
Outcome [n (%)]	
Survival	42 (84)
Death	8 (16)

APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; LMWH, low-molecular-weight heparin; MODS, multiple organ dysfunction score; MV, mechanical ventilation; RICU, respiratory intensive care unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; UFH, unfractionated heparin; VAP, ventilator-associated pneumonia, [a]Data in parentheses represent median.

four patients, and three of them were patients with thrombocytopenia. All patients under study were receiving drugs that cause thrombocytopenia: 14 patients received unfractionated heparin (UFH) and 11 patients received low-molecular-weight heparin (LMWH); drugs inducing thrombocytopenia other than UFH and LMWH included antimicrobials (penicillin, cephalosporins, rifampicin, vancomycin), NSAIDs, and antacids (ranitidine).

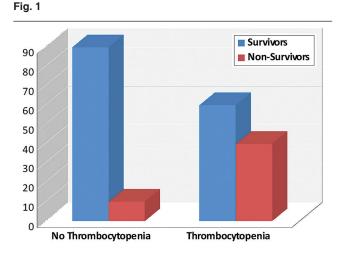### Risk factors associated with the development of thrombocytopenia

The thrombocytopenic group had a higher mortality (40 vs. 10%, $P < 0.05$), a lower admission platelet count (215.3 ± 85.6 vs. 252.8 ± 73.2, $P < 0.05$), a lower nadir platelet count (111.1 ± 22.6 vs. 213.9 ± 53.2, $P < 0.001$), increased transfusion requirement (30 vs. 2.5%, $P < 0.05$), and increased septic shock (40 vs. 2.5%, $P < 0.05$) compared with the nonthrombocytopenic group. No significant difference was observed between the two groups ($P > 0.05$) in terms of age, sex, comorbidities, indication for RICU admission, the length of RICU stay, MV, days on MV, admission severity scores, baseline hemoglobin, the baseline total leukocytic count, bleeding, ventilator-associated pneumonia, acute respiratory distress syndrome, and medications administrated during the RICU stay (Table 2, Figs 1 and 2). When a cutoff of 15 days was used for the length of RICU stay, the difference was statistically significant between thrombocytopenic and nonthrombocytopenic patients ($P = 0.046$), and the risk of having thrombocytopenia among cases staying more than 15 days in RICU was 4.7 times higher.
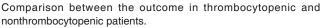
Factors affecting the outcome

Only thrombocytopenia affected the outcome of patients: thrombocytopenia increases significantly among nonsurvivors ($P = 0.041$). Other variables including MV and admission severity scores did not differ significantly (Table 3).

Risk factors for ICU-acquired mortality

The effect of various independent factors on the primary outcome mortality was investigated using a multivariate analysis: thrombocytopenia was the only independent factor affecting mortality. Other independent factors including APACHE II, SOFA, SAPS II, and MODS did not significantly affect mortality ($P > 0.05$, Table 4).
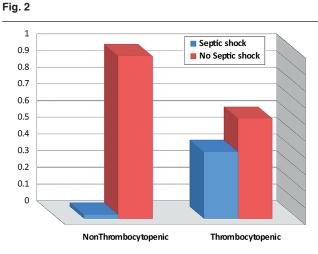
Discussion

Although thrombocytopenia appears as a common finding in the ICU, yet it is still unclear whether thrombocytopenia is the cause or just a risk factor for ICU-related mortality. The present study demonstrated that the incidence of thrombocytopenia of at least one platelet count of less than $150 \times 10^9/l$ was 20% among medical patients in RICU. A wide range for the incidence of thrombocytopenia has been presented in previous studies (13–44.1%) [4,6,9]; some results were comparable among the medical-surgical adult ICU (22.6%) [9] and the pediatric ICU (19.6%) [14]. Relatively higher results were obtained in medical adult ICUs (37.1%) [15], medical-surgical adult ICUs (40%) [16], a predominantly medical adult ICU (41%) [3], and medical adult ICUs (44%) [4]. Different types of patients under study as well as differences in the cutoff for defining thrombocytopenia likely explain this wide variation.

The primary outcome in this study was ICU mortality, which occurred in 16% of the cases, including 40% of thrombocytopenic patients compared with 10% of nonthrombocytopenic patients. Thus, mortality was significantly higher in the thrombocytopenic group. Similar results were obtained in other studies [3,4,8,9,14–16]. Possible explanations for the increased mortality in patients with thrombocytopenia include the following: first, thrombocytopenia is a marker of severe organ dysfunction, which is frequently seen in patients with a greater disease severity. Second, many instances of thrombocytopenia are associated with the underlying disease processes that necessitated intensive care. Third, thrombocytopenia is associated with hemostatic derangement and the complications associated with this condition such as bleeding, transfusion, and thrombosis, which may adversely affect the patient's prognosis [15].

Fig. 1

Comparison between the outcome in thrombocytopenic and nonthrombocytopenic patients.

Fig. 2

Distribution of septic shock in the study population.

Thrombocytopenia commonly results in bleeding. Accordingly, the incidence of bleeding in this study was 5% of the nonthrombocytopenic patients, but this incidence increased to 40% in patients with thrombocytopenia. All patients with thrombocytopenia who developed bleeding had a platelet count greater than 100×10^9/l on the days of occurrence of bleeding, except for one patient whose platelet count was less than 100×10^9/l on the days of bleeding. This observation was documented in another study, and a reasonable explanation was presented this study [3] through the assumption that factors other than the absolute platelet count, including associated disorders of coagulation or of

platelet function and the rate and direction of change in platelet count [17,18], must be considered in assessing bleeding risk in thrombocytopenia patients. Another study in patients with hematological disorders and severe thrombocytopenia found that the mean platelet volume predicted bleeding more reliably than the platelet count [19].

Sepsis was found to be the most common risk factor for the development of thrombocytopenia in the ICU in several studies [2,5,8,20]. In our study, sepsis as an indication for RICU admission did not differ significantly between patients with or without RICU-acquired thrombocytopenia

Table 2 A comparison between thrombocytopenic and nonthrombocytopenic patients

Variables	No thrombocytopenia (n = 40)	Thrombocytopenia (n = 10)	P
Age[a] (years)	55.0 ± 15.2	51.6 ± 12.6	0.521
Sex [n (%)]			
Male	23 (57.5)	6 (60)	1
Female	17 (42.5)	4 (40)	
Admission APACHE II[a]	19.9 ± 9.8	21.6 ± 9.4	0.613
Admission SOFA[a]	5.3 ± 4.7	4.9 ± 2	0.782
Admission SAPS II[a]	40.1 ± 13.8	40 ± 9.7	0.983
Admission MODS II[a]	5.8 ± 3.2	6.5 ± 2.5	0.529
Days in RICU[a]	8.9 ± 5.6	23 ± 24	0.096
Days in RICU [n (%)] (days)			
≤15	33 (82.5)	5 (50)	0.046
>15	7 (17.5)	5 (50)	
MV [n (%)]	22 (55)	9 (90)	0.067
Days on MV[a]	7.09 ± 6.34	21.56 ± 24.04	0.06
Hemoglobin[a]	12.5 ± 2.6	13.3 ± 3	0.457
Total leukocytic count[a]	12.5 ± 6.3	11.7 ± 4.5	0.688
Indication for RICU admission [n (%)]			
Respiratory failure	26 (65)	6 (60)	0.941
Sepsis	4 (10)	3 (30)	0.133
Lung mass	1 (2.5)	0 (0)	1
Pleural disease	4 (10)	0 (0)	0.571
Pulmonary embolism	1 (2.5)	1 (10)	0.363
Cardiac disease	4 (10)	0 (0)	0.571
Use of drug-induced thrombocytopenia [n (%)]			
UFH + others	10 (25)	4 (40)	0.436
LMWH + others	9 (22.5)	2 (20)	1
Others	21 (52.5)	4 (40)	0.725
Thrombocytopenia [n (%)]			
Platelet count on admission[a]	252.8 ± 73.2	215.3 ± 85.6	0.032
Nadir platelet count[a]	213.9 ± 53.2	111.1 ± 22.6	0.0001
Blood transfusion [n (%)]	1 (2.5)	3 (30)	0.022
Complications [n (%)]			
Bleeding	2 (5)	4 (40)	0.6
VAP	1 (2.5)	0 (0)	1
ARDS	1 (2.5)	2 (20)	0.098
Septic shock	1 (2.5)	4 (40)	0.004
Outcome [n (%)]			
Survival	36 (90)	6 (60)	0.041
Death	4 (10)	4 (40)	

APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; LMWH, low-molecular-weight heparin; MODS, multiple organ dysfunction Score; MV, mechanical ventilation; RICU, respiratory intensive care unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; UFH, unfractionated heparin; VAP, ventilator-associated pneumonia; [a]Data in parentheses represent median; [a]Data represent mean ± SD.

Table 3 A comparison between patients' outcomes regarding selected variables

Variables	Outcomes		P
	Survivors (*n* = 42)	Nonsurvivors (*n* = 8)	
Thrombocytopenia [*n* (%)]	6 (14.3)	4 (50)	0.041
MV [*n* (%)]	24 (57.1)	7 (87.5)	0.134
APACHE II (mean ± SD)	24.54 ± 7.36	24.43 ± 11.73	0.975
SOFA (mean ± SD)	6.67 ± 5.29	6.86 ± 2.85	0.190
SAPS (mean ± SD)	43.92 ± 10.27	50.43 ± 18.70	0.235
MODS (mean ± SD)	6.92 ± 2.34	8.71 ± 3.99	0.141

APACHE, acute physiology and chronic health evaluation; MODS, multiple organ dysfunction score; MV, mechanical ventilation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

Table 4 Multivariate analysis for the effect of independent variables on mortality

Variables	95% CI	OR	P
Thrombocytopenia	1.213–13.081	141.068	0.034
APACHE II	0.635–0.806	1.024	0.078
SOFA	0.62–1.022	1.685	0.932
SAPS	0.899–1.057	1.242	0.503
MODS	0.931–2.014	4.357	0.075

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; MODS, multiple organ dysfunction Score; OR, odds ratio; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

possibly because only seven patients were admitted to the RICU because of sepsis; these findings have not been consistent among different studies [4,14], possibly because these studies might have included more patients with sepsis. Septic shock, a RICU-acquired complication, was more common among patients with thrombocytopenia, suggesting a possible important risk factor for the development of thrombocytopenia. Our study has revealed that severity scores did not differ significantly between nonthrombocytopenic and patients with thrombocytopenia. This observation is in accordance with the insight that such scores are static, their mortality predictions based on the worst values of selected variables recorded during the initial 24 h of admission to the ICU. Consequently, these severity scoring systems do not take into consideration subsequent changes caused by the natural course of the disease or by therapy [3]. Although the authors developing MODS found that the increase in MODS over the course of ICU stay correlated better with the ICU mortality rate than the admission severity indices [13], yet only admission MODS was available in our study without daily MODS over the entire ICU period. Thus, the outcome was not only a function of the severity of the admission illness,

but also of the degree of functional deterioration developed by the patient during the ICU stay period.

Although the mean length of RICU stay was not among the risk factors for the development of thrombocytopenia, yet when considering a cutoff of more than 15 days, patients were 4.7 times more at risk for the development of thrombocytopenia than patients staying in the RICU for less than 15 days.

Many drugs commonly used in the ICU can cause thrombocytopenia, and most ICU patients receive a large number of different drugs [21]. Heparin-induced thrombocytopenia is a well-described complication of heparin therapy with an incidence of 1–5% when UFH is used, but less than 1% with LMWH [22]. Surprisingly, the intake of drugs causing thrombocytopenia in our study carried no significant difference between thrombocytopenic and nonthrombocytopenic patients. These results were similar to other study [4] where the administration of drugs including heparin, penicillin, cephalosporins, and proton pump inhibitors was not.

Many previous studies have reported an association between thrombocytopenia and poor outcomes [3,9,15,23]. Our study revealed that only thrombocytopenia differed significantly between survivors and nonsurvivors. Other studies [4,14] showed a similar significant association between mortality and platelet counts, and yet in one of these studies [4], the APACHE II score differed significantly between survivors and nonsurvivors. This discrepancy could be attributed to the daily recording of APACHE II scores in this study rather than the admission APACHE II score recorded in our study. The impact of thrombocytopenia significantly affected the outcome of patients in our study. Similarly, other studies on thrombocytopenia reported that thrombocytopenia is recognized as an independent risk factor for mortality in ICU patients [3,5,7,9].

This study has the advantage of excluding patients with thrombocytopenia on admission to the RICU to evaluate the effect of the RICU on the development of thrombocytopenia. Moreover, the patients under study were medical RICU patients excluding the highest risk for the development of thrombocytopenia seen in other patients, especially in trauma cases.

In conclusion, thrombocytopenia is common in critically ill patients admitted to the RICU and was associated with increased mortality. Moreover, thrombocytopenia represents an independent predictor for mortality. Prolonged ICU stay and septic shock are among the risk factors for developing thrombocytopenia.

Finally, the recording of the baseline platelet count for critically ill patients admitted to the ICU is recommended with further continuous monitoring of the platelet count during the whole ICU stay, especially for patients with septic shock and for those with a prolonged ICU stay.

Acknowledgements
Conflicts of interest

References

1 Baughman RP, Lower EE, Flessa HC, et al. Thrombocytopenia in the intensive care unit. Chest 1993; **104**:1243–1247.

2 Bonfiglio MF, Traeger SM, Kier KL, et al. Thrombocytopenia in intensive care patients: a comprehensive analysis of risk factors in 314 patients. Ann Pharmacother 1995; **29**:835–842.

3 Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000; **28**:1871–1876.

4 Strauss R, Wehler M, Mehler K, et al. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002; **30**:1765–1771.

5 Stephan F, Hollande J, Richard O, et al. Thrombocytopenia in a surgical ICU. Chest 1999; **115**:1363–1370.

6 Hui P, Cook DJ, Lim W, et al. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. Chest 2011; **139**:271–278.

7 Akca S, Haji-Michael P, de Mendonça A, et al. Time course of platelet counts in critically ill patients. Crit Care Med 2002; **30**:753–756.

8 Shalansky SJ, Verma AK, Levine M, et al. Risk markers for thrombocytopenia in critically ill patients: a prospective analysis. Pharmacotherapy 2002; **22**:803–813.

9 Crowther MA, Cook DJ, Meade MO, et al. Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. J Crit Care 2005; **20**:348–353.

10 Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; **13**:818–829.

11 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; **22**:707–710.

12 Le Gall JR, 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.

13 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.

14 Agrawal S, Sachdev A, Gupta D, et al. Platelet counts and outcome in the pediatric intensive care unit. Indian J Crit Care Med 2008; **12**:102–108.

15 Lim SY, Jeon EJ, Kim HJ, et al. The incidence, causes, and prognostic significance of new-onset thrombocytopenia in intensive care units, a prospective cohort study in a Korean hospital. J Korean Med Sci 2012; **27**:1418–1423.

16 Kurian S, Mehta A, Shibli MH. Prognostic power of thrombocytopenia in critically ill patients. Chest 2009; **136**:28S.

17 Platelet transfusion therapy. JAMA 1987; **257**:1777–1780.

18 Beutler E. Platelet transfusions: the 20 000/microL trigger. Blood 1993; **81**:1411–1413.

19 Eldor A, Avitzour M, Or R, et al. Prediction of haemorrhagic diathesis in thrombocytopenia by mean platelet volume. Br Med J 1982; **285**:397–400.

20 Cawley MJ, Wittbrodt ET, Boyce EG, et al. Potential risk factors associated with thrombocytopenia in a surgical intensive care unit. Pharmacotherapy 1999; **19**:108–113.

21 Bogdonoff D, Williams M, Stone D Thrombocytopenia in the critically ill patient. J Crit Care 1990; **3**:186–205.

22 Warkentin TE, Cook RJ, Marder VJ, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. Blood 2005; **106**:3791–3796.

23 Sprung CL, Peduzzi PN, Shatney CH, et al. Impact of encephalopathy on mortality in the sepsis syndrome. The Veterans Administration Systemic Sepsis Cooperative Study Group. Crit Care Med 1990; **18**:801–806.