Peer reviewed article

Is the fall in platelet count associated with intensive care unit acquired pneumonia?

I. Kivilcim Oguzulgen, Turkan Ozis, Gul Gursel

Gazi University School of Medicine Department of Pulmonary Medicine, Ankara, Turkey

Summary

Principles: Intensive Care Unit Acquired Pneumonia is the most frequent infection among patients receiving mechanical ventilation and has an important impact on patient mortality. Thrombocytopenia is one of the most common laboratory abnormalities in Intensive Care Unit (ICU). The aim of this study was to evaluate the relationship between platelet count and Intensive Care Unit Acquired Pneumonia (ICUAP).

Methods: Medical records of 41 mechanically-ventilated pulmonary ICU patients having at least one ICUAP were reviewed. The date of first ICUAP, etiologic pathogens, platelet count at admission, the nadir value within seven days before and after the date of ICUAP, development of thrombocytopenia (platelet $<100 \times 10^3/mm^3$), acute physiology and chronic health evaluation (APACHE) II scores on admission, medications and events that can effect platelet count and other laboratory values were noted.

Results: The meantime for the first ICUAP was 13 ± 10.3 days after ICU admission. The nadir platelet count associated with ICUAP (ICUAP-platelet count) was seen on 12.1 ± 11.3th day after ICU admission; with a significant fall (30% fall) when compared to admission platelet count (platelet counts are 157.2 ± 87.4 × $10^3/mm^3$, 224.1 ± 106.3 × $10^3/mm^3$ respectively, $p < 0.001$). Fifteen of the 41 patients had an episode of thrombocytopenia during their ICU stay and these patients had a higher mortality rate than nonthrombocytopenics (mortality rates are 80% and 50% respectively, $p = 0.05$).

Conclusion: Besides the proven role of thrombocytopenia in prognosis in ICU, the significant fall in platelet count can be an early warning parameter and possible diagnostic hint for severe infections in ICU such as ICUAP.

Key words: thrombocytopenia; platelets; intensive care unit acquired pneumonia; ventilator associated pneumonia (VAP)

Introduction

Ventilator Associated Pneumonia (VAP) or as recently called Intensive Care Unit Acquired Pneumonia (ICUAP) is the pneumonia that may occur as early as within the first 48 hours after intubation [1] and is the most frequent infection among patients receiving mechanical ventilation. ICUAP not only prolongs the duration of mechanical ventilation but also increases the mortality rate [1–3].

Thrombocytopenia is one of the most common laboratory abnormalities among Intensive Care Unit (ICU) patients. It is difficult to determine the cause of thrombocytopenia in ICU and it is often multi-factorial. Whatever the cause, thrombocytopenic patients are shown to have higher mortality rates and longer hospital stays [4–6]. The aim of this study was to evaluate the relationship between platelet count and ICUAP.

Methods

Medical records of mechanically-ventilated patients followed-up in our pulmonary ICU between February 2001 and March 2003 were reviewed. Forty-one patients having ICUAP were enrolled in the study. The first ICUAP episode after ICU admission was taken into account. The following information was recorded: 1) age, gender, the cause of ICU admission, prognosis and the length of ICU stay, 2) the onset day of first ICUAP and the etiologic pathogens, 3) platelet count at admission, the nadir platelet count within seven days before and after the date of ICUAP (ICUAP associated nadir platelet count: ICUAP-platelet count), development of thrombocytopenia during ICU stay, 4) acute physiology and chronic health evaluation (APACHE II) score [7] on admission, 5) clinical pulmonary infection score (CPIS) on the day of onset of ICUAP [8], 6) the sepsis-related organ failure

No financial support declared.

assessment (SOFA) score on the onset day of ICUAP [9] 7) presence of sepsis and overt disseminated intravascular coagulation (DIC) (before or within 48 h after the diagnosis of ICUAP), 8) presence of monitoring equipment, *ie*, arterial catheter, central venous catheter, 9) drugs ordered for at least four days during the first week or a week before the ICUAP episode that can alter platelet counts, *ie*, unfractionated or low-molecular-weight heparin, H_2-antagonist, furosemide, beta-lactam antibiotics, teicoplanin, piperacillin-tazobactam 10) blood transfusions 11) laboratory values including complete blood count, coagulation parameters on the onset day of ICUAP 12) the presence of an infection other than ICUAP.

Definitions

ICUAP: The diagnosis was made in the presence of both microbiological confirmation [growth of $>10^{-5}$ colony-forming units/mL of microorganism on endotracheal aspirate (ETA)], and clinical criteria: a new radiological infiltrate after being in hospital for more than 72 h and two of the following: a) body temperature >38° C or <35 °C; b) white blood cells >10,000/mm^3 or <3000/mm^3; c) macroscopically purulent tracheal aspirate [3].

Onset day of ICUAP: Regular ETA cultures were taken every second or third day in ICU and also at the time of suspicion of pneumonia. Within the definition of ICUAP above, in the presence of consistent clinical findings, the day the positive ETA culture was taken was considered the onset day of ICUAP.

Thrombocytopenia: Platelet counts were determined daily throughout the ICU stay by an automated cell counter. Thrombocytopenia was defined as a platelet count $<100 \times 10^3$/mm^3.

Sepsis: The criteria for sepsis used in this study have been previously reported [10].

DIC: Overt DIC was defined as reported by Taylor Jr et al. [11]. In the presence of a severe infection known to be associated with DIC (in this study ICUAP); platelet count, D-Dimer, prolongation of prothrombin time and fibrinogen levels were scored as reported.

Statistics

Data were analysed by using SPSS for windows release 10.0.1 (SPSS, Chicago, IL). Values were expressed as mean ± SD. Continuous variables were compared with Student's *t*-test for normally distributed variables and the Mann-Whitney U test for nonnormally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. The Spearman test was used for correlations. All *p* values were two-tailed, and a *p* of <0.05 was considered statistically significant.

Results

In this series of 41 patient the most common etiologic factor for ICU admission was chronic obstructive pulmonary disease (COPD). Patient characteristics are seen in table 1. No source of infection was found other than ICUAP in the study population during the study period.

ICUAP-platelet count was seen on the 12th day after admission, one day before the onset of ICUAP, and there was a significant fall (30% fall) when compared to the admission platelet count ($p < 0.001$) (figure 1). The median value for ICUAP-platelet was 138×10^3/mm^3 and only eleven of 41 patients had ICUAP-platelet $<100 \times 10^3$/mm^3.

Single microorganisms were identified in 36 of

Table 1

Patient characteristics.

Clinical features	(n: 41)
Sex M/F	14 / 27
Age, yr	70.4 ± 13.0
Aetiologic factor for ICU admission	
COPD	16 (39%)
Community Acquired Pneumonia	11 (26.8%)
Neuromuscular disease	4 (9.8%)
Asthma	3 (7.3%)
Congestive heart failure	2 (4.9%)
Bronchiectasis	1 (2.4%)
Pulmonary Thromboembolism	1 (2.4%)
Obesity hypoventilation	1 (2.4%)
Idiopathic Pulmonary Fibrosis	1 (2.4%)
Lung Cancer with obstructive pneumonia	1 (2.4%)
Time between ICU admission and first ICUAP* (days)	13.0 ± 10.3
Time between ICU admission and the occurrence of ICUAP-platelet** (days)	12.1 ± 11.3
APACHE II score on admission	18.9 ± 5.2 (n: 35)
CPIS at the time of ICUAP	7.9 ± 2.2 (n: 37)
SOFA score at the time of ICUAP	4.7 ± 2.1 (n: 38)
Total length of ICU stay (days)	28.9 ± 10.0
Prognosis (survivors/nonsurvivors)	16 / 25

* ICUAP: ICU acquired pneumonia
** ICUAP-platelet: ICUAP associated nadir platelet count

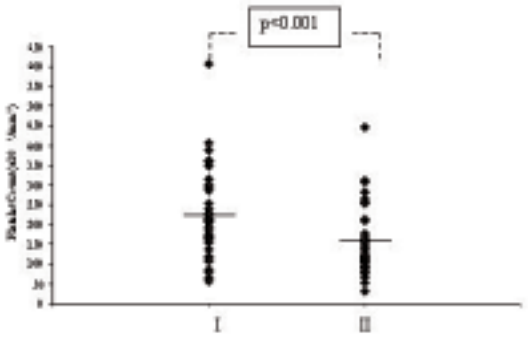


Figure 1

Platelet counts at Intensive Care Unit (ICU) admission (I) and the nadir platelet count associated with Intensive Care Unit acquired pneumonia (ICUAP-platelet count) (II), (Small horizontal lines indicate the mean values: $157.2 \pm 87.4 \times 10^3/mm^3$, $224.1 \pm 106.3 \times 10^3/mm^3$ respectively).

*p<001 by Student'st-test (Plt counts at ICU admission versus the ICUAP-plt count)

the 41 ICUAP episodes, while the five remaining patients had mixed infections with both gram-negative and positive microorganisms. In this group of 36 patients with ICUAP caused by a single microorganism, gram-positive pathogens were identified in 13 patients *(methicillin-resistant Staphylococcus aureus)*, while gram-negatives were identified in 23 patients (*Pseudomonas aeruginosa* [n: 11], *Acinetobacter spp*. [n: 10], *Klebsiella spp.* [n: 2]). There was no significant difference in ICUAP-platelet counts or the percent of the fall in platelet counts between the patients with ICUAP caused by gram-negative microorganisms when compared to ICUAP caused by gram-positive microorganism (table 2).

As this was a retrospective study 33 patients out of 41 had all the data for the evaluation of sepsis and 32 had positive criteria for sepsis at the onset of ICUAP. Missing data for the evaluation of overt-DIC was less. Twenty-six out of 37 had positive criteria for overt-DIC. When we compare the 26 patients having overt-DIC with the 11 without overt-DIC; both groups had a fall in platelet counts before the diagnosis of ICUAP. The percent of the fall was higher in overt-DIC-positive group (35%, 15.3% in overt-DIC-positive and negative groups respectively p = 0.05).

The mean CPIS score was 7.9 ± 2.2 supporting the diagnosis of ICUAP. SOFA scores were negatively correlated with ICUAP-platelet count (r = –0.67, p <0.001).

Twenty-one patients received low molecular weight heparin starting on admission day in the ICU. There were no significant differences in ICUAP-platelet counts or the percentage of the fall in platelet counts when compare to admission values between heparin treated patients and the others (p >0.05). Yet, no significant effect of any other mentioned drugs or blood transfusions to platelet counts were noticed.

In seven patients of the study population there was no fall in ICUAP-platelet count when compared to ICU admission platelet count. No difference was found between these two groups in relation to the mentioned medications used that could alter platelet counts, etiologic factors for ICU admission and APACHE scores (p >0.05).

All the patients had arterial and central venous catheters after ICU admission.

Fifteen patients (36.5% of the study population) had an episode of thrombocytopenia during their whole ICU stay and these patients had higher mortality rate than nonthrombocytopenics (mortality rates are 80% and 50% respectively, p = 0.05).

Table 2

Platelet counts in ICUAP caused by gram-negative and gram-positive microorganisms in 36 patients with ICUAP caused by a single microorganism.

	ICUAP caused by Gram (+) microorganisms	ICUAP caused by Gram (-) microorganisms	p
Admission platelet count	$197.3 \pm 93.3 \times 10^3/mm^3$	$240.9 \pm 107.3 \times 10^3/mm^3$	NS*
ICUAP-platelet count**	$144.6 \pm 66.0 \times 10^3/mm^3$	$169.9 \pm 103.7 \times 10^3/mm^3$	NS

* NS: Not significant

** ICUAP-platelet: ICUAP associated nadir platelet count

Discussion

ICUAP complicates the course of patients receiving mechanical ventilation at a serious rate. Diagnosing ICUAP is still confusing because of the problems in distinguishing colonisation of respiratory tract with potential pulmonary pathogens from infection in mechanically ventilated patients and the absence of a clinically gold standard [2].

Thrombocytopenia occurs frequently in ICU patients. This probably reflects the severity of the disease and has even been suggested to be indicative of acute infection [4]. In this study we found an earlier significant fall in platelet count before the onset of ICUAP.

The causes of the fall in platelet count and thrombocytopenia in critically ill patients has been widely studied in various studies. Sepsis, DIC, ARDS, drugs, invasive monitoring devices and transfusions are the most accused factors [4, 5, 12–16]. It has been shown that thrombocytopenia can occur in infections caused by various pathogens but the presence of sepsis was shown to be the main risk factor [12, 14]. The major cause of platelet destruction in sepsis is suggested to be the haemophagocytosis associated with high macrophage-colony stimulating factor concentrations [12, 14, 16, 17]. In our study 32 patients out of 33 who had full data, had positive criteria for sepsis. But only a minority of the patients (nine of

32 patients with sepsis and 11 of the whole study population) had ICUAP-platelet count <100 × 10^3/mm^3, which is defined as thrombocytopenia. Consequently we cannot claim that sepsis is fully responsible for the fall in platelet counts in this study; furthermore, our sepsis definition doesn't contain thrombocytopenia (10). However, the study would have been more indicative if we could have had a sepsis-negative group.

Another explanation for the fall in platelet count could be the bacteria-platelet interaction. It has been demonstrated that human platelets are rapidly bound and aggregated in vitro by some gram negative and positive pathogens [18]. Some investigators have shown that this platelet-bacteria interaction leads to thrombocytopenia [19].

Recently it has been suggested that a significant increase in bronchoalveolar thrombin generation was observed in patients with ICUAP which possibly lead to platelet consumption [20].

We found that the mean nadir platelet count associated with ICUAP emerged earlier than the clinical diagnosis of ICUAP and this was the interesting point of this study. The significant fall in platelet count can be considered a sign of non-overt acute infection probably complicated by sepsis.

DIC could also contribute to the increased platelet consumption, but this was not the case in our study as patients having overt-DIC had only some additional platelet fall, this is also supported by François et al. [17].

Mavrommatis et al in their controlled study showed that in 74 septic patients platelets were reduced and all changes were independent of the causative infectious pathogen. Gram-positive, gram-negative and other microorganisms produce identical impairment of coagulation [21]. Like in the mentioned study, we found no significant difference in the percent decrease of platelet count between gram-negative and gram-positive ICUAP.

Event hough some drugs are shown to increase platelet destruction, in most of the ICU studies drugs were not found to be a significant risk factor in multivariate analysis [4, 6, 15, 22]. Here also we found that drugs did not have any effect on platelet count. As all the patients had central venous and arterial catheters an effect on platelet destruction was excluded.

To assess the severity of illness in ICU patients, classification systems like APACHE II and SOFA are commonly used. Thrombocytopenia was associated with the most severely ill patients, it has a prognostic value independent and complementary to the APACHE II and reflected by a higher APACHE II score [4, 5, 23]. Declining platelet counts predicted mortality as reliably as did SOFA or APACHE II scores in some studies [22]. We found a negative significant correlation between the ICUAP-platelet and SOFA scores.

We also showed that having an episode of thrombocytopenia was associated with a higher mortality rate, which has been reported previously [4, 6, 22, 24].

The most important limitation of our study is its retrospective design. A prospective study design with a control group having other or no ICU infection would have been more valuable in confirming the relationship between platelets in ICUAP and the role of sepsis. Although thrombocytopenia has been described in patients with infections and sepsis, this study is to our knowledge, the first report on the relationship between the early fall in platelet count and development of pneumonia in the ICU.

In conclusion, platelets could be a reliable monitoring parameter in ICU and could complement scoring systems. The fall in platelet count can be an early warning parameter and possible diagnostic hint for severe ICU infections like ICUAP, the most common nosocomial infection in ICU.

Correspondence:
I. Kivilcim Oguzulgen
Turan Gunes Bulvari 92/2
TR-06550 Cankaya, Ankara
Turkey
E-Mail: ipek@gazi.edu.tr

References

1 Chastre J, Fagon JY. Ventilator-associated Pneumonia. Am J Respir Crit Care Med 2002;165:867–903.
2 Dennesen PJ, van der Ven AJ, Kessels AG, Ramsay G, Bonten MJ. Resolution of Infectious Parameters after Antimicrobial Therapy in Patients with Ventilator-associated Pneumonia. Am J Respir Crit Care Med 2001;163:1371–5.
3 Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, et al. Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 2003;31:676–82.
4 Stephan F, Hollande J, Richard O, Cheffi A, Maier-Redelsperger M, Flahault A. Thrombocytopenia in Surgical ICU. Chest 1999;115:1363–70.
5 Vanderschueren S, de Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A, et al. Thrombocytopenia and prognosis intensive care. Crit Care Med;28:1871–6.
6 Baughman RP, Lower EE, Flessa HC, Tollerud DJ. Thrombocytopenia in the Intensive Care Unit. Chest 1993;104:1243–7.
7 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818–29.
8 Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991;143:1121–9.
9 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure: on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.

10 Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, et al. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: Time for a reevaluation. Crit Care Med 2000;28:232–5.
11 Taylor Jr FB, Toh CH, Hoots WK, Wada H, Levi M. Towards Definition, Clinical and Laboratory Criteria, and a Scoring System for Disseminated Intravascular Coagulation. Thromb Haemost 2001;86:1327–30.
12 Stephan F, Montblanc J, Cheffi A, Bonnet F. Thrombocytopenia in critically ill surgical patients: a case-control study evaluating attributable mortality and transfusion requirements. Crit Care 1999;3:151–8.
13 George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, et al. Drug-Induced Thrombocytopenia: A Systemic Review of Published Case Reports. Ann Intern Med 1998;129:886–90.
14 George JN. Platelets. Lancet 2000;355:1531–9.
15 Wade EE, Rebuck JA, Healey MA, Rogers FB. H2 Antagonist-induced thrombocytopenia: is this a real phenomena? Intensive Care Med 2002;28:459–65.
16 Stephan F, Thioliere B, Verdy E, Tulliez M. Role of Hemophagocytic Histiocytosis in the Etiology of Thrombocytopenia in Patients with Sepsis Syndrome or Septic Shock. Clinical Infectious Diseases 1997;25:1159–64.
17 François B, Trimoreau F, Vignon P, Fixe P, Praloran V, Gastinne H. Thrombocytopenia in the Sepsis Syndrome: Role of Hemophagocytosis and Macrophage Colony-stimulating Factor. Am J Med 1997;103:114–20.
18 Yeaman MR, The role of platelets in antimicrobial host defense. Clin Infect Dis 1997;25:951–70.
19 Spika JS, Peterson PK, Wilkison BJ, Hammerschmidt DE, Verbrugh HA, Verhoef J, et al. Role of peptidoglycan from *Staphylococcus aureus* in leukopenia, thrombocytopenia and complement activation associated with bacteriemia. J Infect Dis 1982;146:227–34.
20 Schultz M, Millo J, Levi M, Garrard C, van der Poll T. Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator-associated pneumonia. Thorax 2004;59:130–5.
21 Mavrommatis AC, Theodoridis T, Orfanidou A, Roussos C, Christopoulou-Kokkinou V, Zakynthinos S. Coagulation system and platelets are fully activated in uncomplicated sepsis. Crit Care Med 2000;28:451–7.
22 Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: Bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002;30:1765–71.
23 Vincent JL, Yagushi A, Pradier O. Platelet function in sepsis. Crit Care Med 2002;30(Suppl.):S313–S317.
24 Akca S, Haji-Michael P, Mendonça A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. Crit Care Med 2002;30:573–756.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

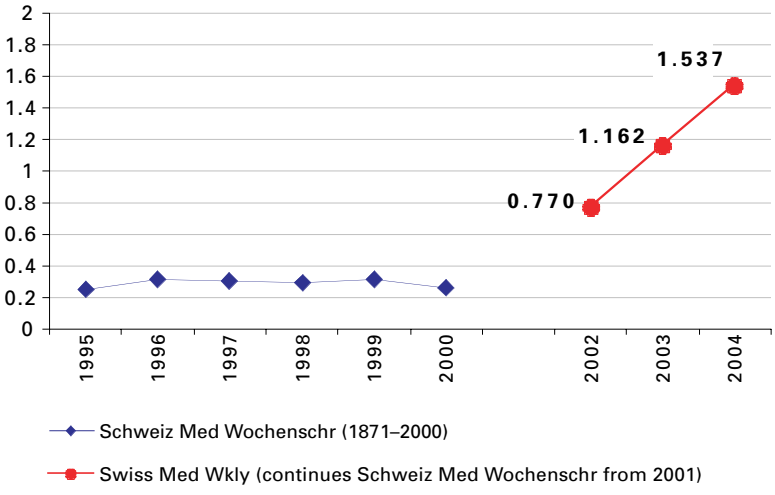
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch