Egyptian Journal of Medical Microbiology Volume 29 / No.1 / January 2020 181-186 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Prevalence and Prognosis of Thrombocytopenia in Blood Culture Proven Neonatal Sepsis

[1] Iman H. Draz, [2]Reham A Dwedar*, [3]Suzan Hagag, [1]Niveen Salama
[1]Pediatrics Department, Faculty of Medicine, Cairo University
[2]Medical Microbiology & Immunology Department, Faculty of Medicine, Cairo University
[3]Public Health and Community Medicine Department, Faculty of Medicine, Cairo University

Key words:
Neonatal sepsis, Thrombocytopenia, Blood culture, Prevalence

Corresponding Author:
Reham Ali Dwedar,
Medical Microbiology & Immunology Department,
Faculty of Medicine, Cairo University
Tel: 01222744624
rehamdwedar@gmail.com

ABSTRACT

Background: *Neonatal sepsis is a major health problem. Thrombocytopenia in neonates is a serious disorder affecting 1%-5% of neonates at birth and up to 50% of the neonates receiving intensive care. Neonates with this disease are at risk for hemorrhage, particularly intraventricular hemorrhage, negative neurodevelopmental outcomes and increased mortality. One of the chief reasons of neonatal thrombocytopenia is sepsis.* ***Objectives****: We aimed to explore the different grades of severity thrombocytopenia and their relationship with diverse types of organisms in blood cultures from neonatal sepsis patients highlighting their prognostic role.* ***Methodology:*** *This is a retrospective study of one year duration including data of culture proven neonatal sepsis patients admitted at the neonatal intensive care unit (NICU), in Cairo University Pediatric Hospital.* ***Results:*** *We studied 314 neonates diagnosed with sepsis grounded on clinical signs and/or microbiological laboratory results. 171 had positive blood culture; 124 of them were Gram negative bacteria (72.5%) and 47 were gram positive ones (24.4%). Klebsiella spp. was the most repeatedly encountered organism among all positive blood cultures (n=74) (43.3%) and coagulase negative staphylococci was the most frequently isolated Gram positive bacteria (n=22) (12.9%). A total of 134 patients had thrombocytopenia; its degree of severity was ranging from mild, moderate, to severe in 101, 25, and 8 neonates, respectively. We found no association between the severity of thrombocytopenia and the type of organism in blood culture; however, thrombocytopenia was significantly higher among neonates with Gram negative blood cultures (p 0.001). Poor outcome has a statistically remarkable correlation with gestational age and reduced platelet count (p value <0.001). There is a 2.131 increased probability of developing thrombocytopenia in patients with neonatal sepsis.* ***Conclusion:*** *The percentage of thrombocytopenia reported in the blood culture proven sepsis episodes highlights the extent of the problem. The present study found a greater percentage of thrombocytopenia among neonates with Gram negative sepsis compared to those with Gram positive sepsis. Sepsis with Klebsiella spp. needs superior consideration regarding platelet monitoring.*

INTRODUCTION

Neonatal sepsis is considered as one of the core health problems all over the world[1]. It is a clinical syndrome in newborns aging 28 days or less which is manifested by different non-specific systemic signs and symptoms reinforced by the isolation of a certain pathogen from the bloodstream[2] . Neonates are highly vulnerable to bacterial sepsis, with its prevalence ranging from 1 to 10 per 1000 live births globally [3]. It is more prevalent in the developing countries where sepsis-linked mortality rate was reported to be 50% [4].

Thrombocytopenia in neonates is a disorder in which the platelet count is less than 150,000/mm[3] regardless of gestational age. It is reported to occur in 1% - 5% of neonates at birth and may reach 50% of the neonates receiving intensive care. Affected neonates are at risk for hemorrhage, particularly intraventricular hemorrhage, negative neurodevelopmental outcomes and elevated mortality[5]. One of the most important origins of neonatal thrombocytopenia is sepsis[6]. However, different degrees of prevalence and severity of thrombocytopenia were described in neonatal sepsis. It was reported that the rate of thrombocytopenia was higher in neonates with late-onset sepsis (59.3%) paralleled with those with early-onset sepsis (24%) also in preterm and low-birth weight neonates [6].

The duration of sepsis-related thrombocytopenia differs according to the causative organisms. For example, patients with fungal and Gram negative sepsis were stated to have thrombocytopenia of longer duration than those with Gram positive sepsis[7]. Moreover, the mortality rate in fungal sepsis patients with thrombocytopenia was reported to be higher than that in fungal sepsis patients without thrombocytopenia [8]. It is also conveyed that the thrombocytopenia related to late-onset sepsis is characterized by being more severe and is associated with higher morbidity and mortality [9].

The current study aimed at exploring the different degrees of thrombocytopenia severity as well as its association with different types of organisms in blood cultures from neonatal sepsis patients.

METHODOLOGY

The present study is a retrospective study of one year duration including retrospectively collected data at the neonatal intensive care unit (NICU), in Cairo University Pediatric Hospital. It was accepted by the institutional ethical committee. Inclusion criteria were the diagnosis of neonates with microbiological bacteremia and/or clinical sepsis associated with non-microbiological laboratory values indicating infections. Neonates were diagnosed of having sepsis if they got a score of 3 or more of the following hematologic findings: i) atypical total leucocyte count, ii) abnormal total polymorphonuclear neutrophils (PMN) count, iii) increased immature PMN count, iv) increased immature to total PMN ratio, v) immature to mature PMN ratio ≥ 0.3, vi) platelets count $\leq$150,000/mm3, and vii) distinct degenerative changes in PMNs [10]. The demographic, clinical, and laboratory data of the neonates enrolled in the study were retrieved from the patients' files in the NICU.

Excluded patients were neonates with other known causes of thrombocytopenia including: maternal thrombocytopenia, Systemic Lupus Erythematosis, preeclampsia and eclampsia, congenital infections, polycythemia, and necrotising enterocolitis along with neonates with intra uterine growth retardation ,resultant from pregnancy induced hypertension or complicated with prenatal TORCH infections.

Sample collection and processing:

Blood samples for culture were acquired aseptically from peripheral veins using butterfly needles (2-3 ml for each sample) and then inoculated into vials which were loaded into BACTEC 9050 instrument as per the manufacturer's instructions (BACTEC- 9050, Beckton-Dickenson, Franklin Lakes, New Jersey, USA). Every vial comprises a sensor that reacts to the concentration of CO_2 formed by the metabolism of microorganisms or the depletion of oxygen required for the growth of microorgnisms. The sensor is checked by the instrument every ten minutes for an intensification in its fluorescence, which is comparative to the cumulative amount of CO_2 or the reducing amount of O_2 present in the vial. A positive reading designates the probable presence of viable microorganisms in the vial. For reporting negative blood culture results, five days protocol was followed. The detection time began with the placement of the bottles in the system and ended with positive signal of instrument, which were additionally proceeded by subcultures on Chocolate agar, blood agar, and MacConkey's agar for 24 hours at 37^{o}C. Further processing was done guided by to the nature of the isolate, as was determined by Gram staining and the colony morphology then essential biochemical tests were accomplished. Gram negative organisms were recognized using oxidase test, triple sugar iron (TSI), citrate utilization, lysin decarboxylation, urea hydrolysis, and indole production. API 20 E identification panel for *Enterobacteriaceae* was utilized for species level identification.

Streptococcus spp. were identified by negative catalase test and bile esculin hydrolysis.

Large colonies (3 to 4 mm in diameter) with a narrow zone of beta-hemolysis that are Catalase negative and bacitracin-resistant were confirmed to be Group B *Streptococci* (GBS) by Streptex latex agglutination (Remmel, UK).

Staphylococcus spp. were distinguished on the basis of positive catalase test, growth on mannitol salt agar, growth on DNAse agar and coagulase test. [11].

The phenotypic test for the recognition of MRSA was done *via* a cefoxitin (30 µg) disc. A zone of inhibition which was equivalent to or more than 22 mm was regarded as susceptible to Cefoxitin and the organism was described as Methicillin Sensitive *Staphylococcus aureus*. Those isolates which produced a zone of inhibition which was less than or equal to 21 mm were considered as Methicillin Resistant *Staphylococcus aureus* (MRSA) [12].

Platelet counts were determined using a coulter counter (Beckman Coulter-COULTER® LH 750 Hematology Analyzer). The platelet counts less than 150,000/mm^3 were re-checked manually. The platelet count samples were taken simultaneously of taking the samples for blood culture. Thrombocytopenia severity was categorized as mild when the platelet count was flanked by 50,000/mm^3 and 150,000/mm^3, moderate when the platelet count was between 20,000/mm^3 and 50,000/mm^3, and severe when the platelet count was <20,000/mm^3 or <50000/mm^3 with clinical bleeding. Platelet transfusions were given if the platelet count was below 20,000/mm^3 or in case of clinical bleeding.

Statistical analysis:

All statistical procedures were conducted using the Statistical Package for Social Science (SPSS for Windows, version 16.0, SPSS Inc., Chicago, Illinois, USA). Descriptive analyses were expressed as

mean ± standard deviation (*SD*) for quantitative variables, and as percentages (%) for categorical variables. Alterations in distribution for categorical variables were accomplished using the Chi square test.

RESULTS

Out of the 935 cases admitted through the study period, 314 neonates (32.9%) were diagnosed with sepsis centered on clinical signs and/or microbiological laboratory results. Sepsis presented more frequently in males than females (178 vs. 136). The characteristics of the study population are clarified in Table (1).

Table 1: Baseline characteristics for the studied neonates

Basic characteristics	No.	%
Gender:		
Male	178	56.7
Female	136	43.3
Gestational age:		
23-28 weeks	22	7.0
28-32 weeks	61	19.4
32-36 weeks	75	23.9
>36 weeks	156	49.7
Referral:		
Home	114	36.3
Same hospital	91	29
Other hospital	109	34.7
Thrombocytopenia:		
Yes	134	42.7
No	180	57.3
Degree of thrombocytopenia:		
Mild	101	75.4
Moderate	25	18.7
Severe	8	6.0
Total	134	100.0

Out of the 314 total patients with neonatal sepsis, 171 had positive blood culture; 124 of them were gram negative bacteria (72.5%) and 47 were Gram positive ones (24.4%), however fungi were not recovered. Table (2) represents the isolated organisms in the studied population. *Klebsiella* spp. was the most recurrent organism among all positive blood cultures (n=74) (43.3%) and Coagulase-negative staphylococci (CoNS) was the most repeated Gram positive bacteria isolated (n=22) (12.9%).

Table 2: Distribution of bacterial growth in blood culture: 124 were Gram negative bacteria (72.5%) and 47 were Gram positive ones (24.4%)

Bacterial pathogens blood isolated from cultures	No.	%
Gram negative pathogens 124 (72.5%)		
***Klebsiella* spp.**	74	43.3
***Pseudomonus* spp.**	18	10.4
***Acinetobacter* spp.**	13	7.6
***Proteus* spp.**	7	4.1
***Salmonella* spp.**	2	1.2
E coli	3	1.8
***Enterobacter* spp.**	5	2.9
***Stenotrophomonas* spp.**	2	1.2
Gram-positive pathogens 47 (24.4%)		
Methicillin Resistant *Staphylococcus aureus* (MRSA)	9	5.3
Group B *Streptococcus* (GBS)	4	2.3
Streptococcus pneumoniae	4	.2.3
Methicillin Sensitive *Staphylococcus aureus* (MSSA)	8	4.7
CoNS	22	12.9
Total	171	100

A total of 134 patients had thrombocytopenia; its degree of severity was mild, moderate, and severe in 101, 25, and 8 neonates, respectively. We found no relationship between the severity of thrombocytopenia and the type of organism in blood culture; however, thrombocytopenia was significantly higher among the neonates with Gram negative blood cultures (*p* 0.001) (Table 3).

Table 3: Distribution of thrombocytopenia among gram negative and positive growth in blood culture:

Blood culture	Thrombocytopenia	P-value
Gram negative n=124	67(54.5%)	0.001
Gram positive n=47	26 (55.3%)	0.057

We noted that poor outcome has a statistically substantial association with gestational age and low platelet count (*p* value <0.001) (Table 4); the more premature and thrombocytopenic the neonate is, the worse the outcome. Six neonates had severe thrombocytopenia, 4 of them were very low birth weight (VLBW). We found no correlation between gestational age and thrombocytopenia (*p*= 0.128) where 71 full term and 63 preterm infants suffered from thrombocytopenia.

There is a 2.131 increased probability of developing thrombocytopenia in patients with neonatal sepsis (Table 5).

Table 4: Outcome of patients in relation to thrombocytopenia and gestational age

Outcome	Dead N (%)	Living N (%)	Total N (%)
Platelet count:			
Normal	26 (14.4)	154 (85.6)	180 (100)
Thrombocytopenia	44 (32.8)	90 (67.2)	134 (100)
Total	70 (22.3)	244 (77.7)	314 (100)
Gestational Age:			
23-28 wks	11 (50.0)	11 (50.0)	22 (100)
28-32 wks	21 (34.4)	40 (65.6)	61 (100)
32-36 wks	16 (21.3)	59 (78.7)	75 (100)
>36 wks	22 (14.1)	134 (85.9)	156 (100)
Total	70 (22.3)	244 (77.7)	314 (100)

Table 5: Logistic regression showing predictors of thrombocytopenia among the studied neonates

Model		B	Sig.	Exp (B)
Step 1	Sex	.209	.369	1.233
	Gestational age	-.023-	.853	.977
	Clinically septic	.757	.011	2.131
	Constant	-.451-	.026	.234

DISCUSSION

Patients with bacterial sepsis associated with thrombocytopenia are at higher risk of mortality [13]. Defining sepsis-related thrombocytopenia in neonates and its features is essential as the incidence of this condition is influenced by several factors. It has been found that thrombocytopenia is a self-regulating risk factor for sepsis-related deaths among VLBW infants [14]. Thrombocytopenia may occur as a result of increased platelets destruction, impaired platelet production, or a blend of both [7, 15, 16]. A previous study by Guida et al. [8]. reported the thrombocytopenia rate to be 54% among VLBW neonates in culture-proven sepsis episodes. Moreover, a significantly higher percentage of thrombocytopenia cases were reported amongst neonates with Gram negative and fungal infections compared to those with gram positive infections. Another study conducted by Charoo et al. [9]. reported that among the patients they enrolled in their study, the rates of thrombocytopenia accompanying sepsis due to CoNS, *Klebsiella* spp., and fungi were 33.3%, 60%, and 66%, respectively. A Spanish study stated that all of their patients with *Candida* sepsis had thrombocytopenia[7]. In addition, an Indian study reported that 59.5% of their nosocomial sepsis patients suffer from thrombocytopenia with diverse degrees of severity at which mild, moderate, and severe thrombocytopenia were reported in 27%, 20%, and 12.5% of the patients, respectively [9].

In the existing study, the blood culture yield is 32.9%. This percentage is comparable to other studies from Egypt[17,18]; however it is lower than a previous report done by El Seifi in 2001 where the rate of sepsis exceeded 50%[19]. This may be attributed to better awareness and adherence to infection control measures.

In the existing study, Gram negative sepsis was the predominant cause of sepsis among our patients (72.5%). This was in agreement with findings of previous studies in literature [20]. In a study conducted by Bhat et al. [13] Gram-negative sepsis, Gram positive sepsis, and fungal sepsis were observed in 71%, 20%, and 8.6% of the examined patients, respectively. Gram negative bacilli were more frequently detected than gram positive cocci, with *Klebsiella pneumoniae* being the most common isolated organism in blood (43,3%). The previous findings agree with several Egyptian studies over two decades as well as other reports from other developing countries [13,17-19]. However, other Egyptian reports demonstrated that the CoNS is the foremost cause of sepsis in 2006 [21]. 2010/2011 [22]. and 2011/2012 [17]. When CoNS is identified in a blood culture, it is challenging to determine whether its growth denotes a true blood stream infection or contamination from skin flora which may lead to clinical uncertainty and potentially extends treatment with antibiotics as well as hospital stay[23].

Unexpectedly we did not meet any invasive candidiasis during the study period.

Although blood cultures remains the gold standard for perceiving candidemia, blood cultures have reduced sensitivity for invasive candidiasis. Blood culture sensitivity is very low in premature infants, where blood culture volumes range from 0.5–1 ml. Depending on blood culture results potentially may lead to under-diagnosis of *Candida* infections and considerably delay initiation of antifungal therapy[24]. Fungal antigen tests and real-time PCR may currently be convincing adjunctive tests and may show promise as early diagnostic tools for neonatal fungal sepsis.

Moreover, we found that among sepsis episodes, thrombocytopenia was detected in 134 neonates (42.6%) with different grades of severity, being mild, moderate, and severe in 101, 25, and 8 patients respectively. Previous studies reported higher rates of thrombocytopenia in sepsis patients as documented by MA Bhat et al.[13]. Guida et al.[8]. and Y Bhat et al. [25]. in which thrombocytopenia was reported in 67%, 71%, and 58.7% of sepsis episodes, respectively.

These findings reveal the high frequency of thrombocytopenia in neonates with sepsis. Neonates' response to sepsis is represented in the up-regulation of Thrombopoietin production and thrombopoiesis; nevertheless, the degree of upregulation is said to be only modest. Thrombocytopenia incidence is expected when the rate of platelet consumption becomes greater than that of platelet production [15].

In this study, a higher number of preterm infants had severe thrombocytopenia compared to full term infants (4 vs 2). In a study by Charoo et al[9], 200 VLBW neonates with sepsis were examined and the percentage of thrombocytopenia was reported to be 59.5%. The increased frequency of thrombocytopenia may be attributed to VLBW neonates' limited response to thrombocytopenia in terms of production of both platelet and Thrombopoietin , particularly during sepsis, because of their decreased energy[26]. Thrombocytopenia rates differ according to sepsis causative microorganisms. In the present study, thrombocytopenia was significantly higher in neonates with gram negative sepsis compared to those with gram positive sepsis (p=0.001).

CONCLUSION

Sepsis is considered as one of the central causes of thrombocytopenia in neonates and the extent of thrombocytopenia varies from mild to severe; this fact demonstrates the importance of close monitoring of platelet count in neonates with sepsis. The percentage of thrombocytopenia reported in the blood culture proven sepsis episodes highlights the magnitude of the problem. The present study found an elevated percentage of thrombocytopenia among neonates with Gram negative sepsis compared to those with Gram positive sepsis. Sepsis with *Klebsiella* spp. needs special attention regarding platelet monitoring.

Conflicts of interest:

- The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

Acknowledgment:

We owe special thanks for Doctor Mahmoud Taha for assisting in data collection.

REFERENCES

1. Afroza S. Neonatal sepsis--a global problem: an overview. Mymensingh medical journal: MMJ. 2006 Jan;15(1):108-14.
2. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine. 2005 Jan 1;6(1):2-8.
1. 3.Mohsen L, Ramy N, Saied D, Akmal D, Salama N, Haleim MM, Aly H. Emerging antimicrobial resistance in early and late-onset neonatal sepsis. Antimicrobial Resistance & Infection Control. 2017 Dec;6(1):63.
3. Edwards MS, Baker CJ. Sepsis in the newborn. In: Gershon AA, Hotez PJ, Katz SL, editors. Krugman's infectious diseases of children. Philadelphia: Mosby; 2004. p. 545.
4. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2003 Sep 1;88(5):F359-64.
5. Khassawneh M, Khader Y, Abuqtaish N. Clinical features of neonatal sepsis caused by resistant Gram-negative bacteria. Pediatrics International. 2009 Jun;51(3):332-6.
6. Torres SC, Dupla MA, Pérez RD, Aliaga YM, Rebage VM. Nosocomial Candida infections and thrombocytopenia in very low birth weight newborns. InAnales de pediatria (Barcelona, Spain: 2003) 2007 Dec (Vol. 67, No. 6, pp. 544-547).
7. Guida JD, Kunig AM, Leef KH, McKenzie SE, Paul DA. Platelet count and sepsis in very low birth weight neonates: is there an organism-specific response?. Pediatrics. 2003 Jun 1;111(6):1411-5.
8. Charoo BA, Iqbal J, Iqbal Q, Mushtaq S, Bhat AW, Nawaz I. Nosocomial sepsis-induced late onset thrombocytopenia in a neonatal tertiary care unit: a prospective study. Hematology/oncology and stem cell therapy. 2009 Apr 1;2(2):349-53.
9. Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. The Journal of pediatrics. 1988 May 1;112(5):761-7.

10. Collee JG and Marr W. Specimen collection,culture containers andmedia. In: Collee JG, Fraser AG, Marmion BP, Simmons A.eds. Mackie & McCartney Practical Medical Microbiology,14th edition New York. Churchill Livingstone, 1996; 85-111.
11. Clinical Laboratory Standards Institute (CLSI) (2019). Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100. Wayne, PA.
12. Bhat MA, Bhat JI, Kawoosa MS, Ahmad SM, Ali SW. Organism-specific platelet response and factors affecting survival in thrombocytopenic very low birth weight babies with sepsis. Journal of Perinatology. 2009 Oct;29(10):702.
13. Ahmad MS, Waheed A. Platelet counts, MPV and PDW in culture proven and probable neonatal sepsis and association of platelet counts with mortality rate. J Coll Physicians Surg Pak. 2014 May 1;24(5):340-4.
14. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2003 Sep 1;88(5):F359-64.
15. Brown RE, Rimsza LM, Pastos K, Young L, Saxonhouse MA, Bailey M, Lawrence RM, Sola-Visner MC. Effects of sepsis on neonatal thrombopoiesis. Pediatric research. 2008 Oct;64(4):399.
16. Moore KL, Kainer MA, Badrawi N, Afifi S, Wasfy M, Bashir M, Jarvis WR, Graham TW, El Kholy A, Gipson R, Jernigan DB. Neonatal sepsis in Egypt associated with bacterial contamination of glucose-containing intravenous fluids. The Pediatric infectious disease journal. 2005 Jul 1;24(7):590-4.
17. El-Din S, Rabie EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of neonatal sepsis and implicated pathogens: a study from Egypt. BioMed research international. 2015;2015.
18. Mohammed D, El Seifi OS. Bacterial nosocomial infections in neonatal intensive care unit, Zagazig University Hospital, Egypt. Egyptian Pediatric Association Gazette. 2014 Sep 1;62(3-4):72-9.
19. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. The Lancet. 2005 Mar 26;365(9465):1175-88.
20. Abd el Haleim MM, Nawar NN, Abd el Rahman EM, Abo Hussein HH, Kamel NR. Epidemiologic and microbacteriologic study of neonatal septicaemia in Cairo University neonatal intensive care units. Res J Med Sci.2009; 4(1):67–77.
21. El Feky EA. Abd el Rahman Z, Mansi YA. Retrospective analysis of neonatal bacteremia and antimicrobial resistance pattern in neonatal intensive care unit. Res J Med Med Sci. 2011;6(2):62-8.23.
22. Hamilton LF, Gillett HE, Smith-Collins A, Davis JW. A Sterile Collection Bundle Intervention Reduces the Recovery of Bacteria from Neonatal Blood Culture. Biomedicine Hub. 2018;3(1):1-7.
23. Hsieh E, Smith PB, Jacqz-Aigrain E, Kaguelidou F, Cohen-Wolkowiez M, Manzoni P, Benjamin Jr DK. Neonatal fungal infections: when to treat?. Early human development. 2012 May 1;88:S6-10.
24. Bhat R, Kousika P, Lewis L, Purkayastha J. Prevalence and severity of thrombocytopenia in blood culture proven neonatal sepsis: A prospective study. Archives of Pediatric Infectious Diseases. 2018 Apr;6(2).
25. Sheu JR, Hung WC, Wu CH, Ma MC, Kan YC, Lin CH, Lin MS, Luk HN, Yen MH. Reduction in lipopolysaccharide-induced thrombocytopenia by triflavin in a rat model of septicemia. Circulation. 1999 Jun 15;99(23):3056-62.