European Journal of Internal Medicine 26 (2015) 782–786

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

D-dimer and histamine in early stage bacteremia: A prospective controlled cohort study

Michael Schwameis [a], Margarete Maria Steiner [a], Christian Schoergenhofer [b], Heimo Lagler [b], Nina Buchtele [a], Petra Jilma-Stohlawetz [c], Thomas Boehm [a], Bernd Jilma [a,*]

[a] Department of Clinical Pharmacology, Medical University of Vienna, 1090 A Vienna, Austria
[b] Department of Internal Medicine I, Medical University of Vienna, 1090 A Vienna, Austria
[c] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Vienna, 1090 A Vienna, Austria

ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form 29 October 2015
Accepted 31 October 2015
Available online 14 November 2015

Keywords:
Bacteremia
Inpatients
D-Dimer
Histamine
Mortality

ABSTRACT

Introduction: Plasma histamine levels and D-dimer predict disease severity and mortality in advanced septic shock. We hypothesized that increased plasma histamine levels parallel coagulation activation and yield prognostic significance already at a very early stage of bacteremia.
Patients and methods: This prospective controlled cohort study enrolled 72 consecutive non-surgical non-ICU-ward inpatients with newly culture-diagnosed bacteremia and a Pitt Bacteremia score ≤2 to determine the extent of histamine and D-dimer release and their predictive role on outcome at the earliest stage of blood stream infection. Age-matched healthy adults served as internal controls ($n = 36$). A binominal logistic regression and a Cox proportional hazards regression analysis were performed to ascertain the effects of D-dimer and histamine on in-hospital mortality.
Results: In contrast to plasma histamine, D-dimer levels were significantly higher within hours of culture-proven bacteremia. In-hospital mortality occurred in 17%. Histamine levels were neither associated with D-dimer level ($r = 0.04$; $p > 0.05$) nor with ICU admissions ($r = 0.06$; $p > 0.05$) and outcome (crude OR 0.8, 95% CI 0.3–1.9; $p = 0.6$). In contrast, early-elevated D-dimer levels predicted mortality: the odds to die increased with the D-dimer level, and was 12.6 (crude OR, 95% CI 3–52; $p = 0.001$) in patients with a D-dimer ≥4 μg/mL ($n = 13$).
Conclusion: Histamine levels are elevated in only few patients (4%) with newly diagnosed bacteremia. Our findings suggest that D-dimer, but not plasma histamine, could be a promising marker of lethality already at a very early stage of blood stream infection.

1. Introduction

D-dimer is a marker of poor outcome in various critical conditions including septic shock [1] and a component of the disseminated intravascular coagulation (DIC) score of the International Society on Thrombosis and Haemostasis (ISTH). Coagulation activation is commonly based on endothelial damage with ensuing exposition of blood to extravascular tissue factor.

Histamine is a classic inflammatory mediator with various functions in antimicrobial host response. Among other actions, it is a potent vasodilator [2] and increases capillary permeability. Several studies support a detrimental effect of histamine in septic syndromes [3]. Histamine contributes to hemodynamic alterations in experimental endotoxemia in rabbits [4] and is associated with mortality in human sepsis [5].

Neutrophils are the critical effectors of the human innate immune system and the first cells recruited into sites of inflammation. Previous studies showed that not merely mast cells but also neutrophils can release high amounts of histamine upon stimulation by bacterial endotoxins and through infection-related complement activation [6–8]. Being a potent leucocyte chemo-attractant [6], neutrophil-derived histamine may early amplify inflammation, contribute to circulatory compromise and promote organ failure in blood stream infections.

As mast cell [9] and complement activation [10] coincide with coagulation activation, a link between histamine and infection-related coagulopathy may be given by histamine's potency to open intercellular tight junctions [11] with ensuing tissue factor exposure to blood and expression [12].

Abbreviations: CVC, central venous catheter; DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; ICU, Intensive Care Unit; LMWH, low molecular weight heparin; NOAC, new oral anticoagulants; SSTI, skin and soft tissue infection; VKA, vitamin K antagonists.

* Corresponding author at: Department of Clinical Pharmacology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Tel.: +43 1 40400 29810; fax: +43 1 40400 29980.
E-mail address: bernd.jilma@meduniwien.ac.at (B. Jilma).

http://dx.doi.org/10.1016/j.ejim.2015.10.024

A small prospective, controlled study investigated plasma histamine levels over five days in patients with overt sepsis, and indicated that histamine values on the first day were highest and best predicted sepsis severity and outcome [5].

Thus, we were interested in whether increased histamine and D-dimer levels are detected even at an earlier stage of infection and compared the predictive value of both in not yet critically ill inpatients with newly diagnosed culture-proven blood stream infection.

We hypothesized that increased plasma histamine levels parallel coagulation activation and may yield prognostic significance already at a very early stage of bacteremia.

2. Patients and methods

The study protocol was approved by the local Ethics Committee and all subjects provided oral and written informed consent. The study was conducted in compliance with the Declaration of Helsinki at the General Hospital of the Medical University of Vienna, a 2100 bed tertiary care facility, from February 2014 to February 2015.

One hundred eighteen consecutive non-surgical, non-intensive care unit (ICU)-ward inpatients ≥18 years with fever (body temperature ≥38.3 °C) and positive bacterial blood culture or LightCycler SeptiFast test result were screened for eligibility. Age-matched adults (n = 36) were used as internal controls to confirm the normal range of plasma histamine levels within the study and to define the assay-specific range of normal values. The primary outcome was the magnitude of histamine release in early bacteremia and its association with D-dimer levels. Secondary outcome was in-hospital mortality. Patients with anaphylaxis, those on histamine receptor blockers, vitamin K antagonists (VKA) or new oral anticoagulants (NOAC), patients with advanced disease severity assessed by the Pitt Bacteremia Score (PBS > 2) and those who underwent surgery within previous three weeks were excluded. Study-related blood sampling was performed immediately after receipt of positive blood-culture result. Parameters documented at time of enrolment are shown in Table 1. The frequency of ICU admissions was recorded and the patients were followed until hospital discharge or death. Coagulation tests were performed as previously described [13] and the ISTH DIC score was calculated as suggested previously [14]. D-dimer levels were measured on the STA-R Evolution analyzer (Diagnostica Stago for Roche Diagnostics GmbH, Germany; normal range < 0.5 μg/mL). Histamine EIA kits were purchased from Immunotech (Beckmann Coulter Company; normal range < 10 nM [nmol/L]). LightCycler SeptiFast test MGRADE (Roche Diagnostics, Germany) and blood cultures (BacT/ALERT FA/FN plus) were processed at the University's Department of Microbiology.

2.1. Statistical analysis

A previous study demonstrated elevated plasma histamine levels in 25% of patients with septic shock [5]. A sample size of n = 72 provided 80% power to detect elevated histamine levels in at least 5% of bacteremia patients. Based on a study on endocarditis patients [15], we determined a sample size of 9 patients per cohort to achieve a 90% power at an alpha error of 2.5% to detect increased D-dimer levels in non-survivors. Study variables are presented as absolute values (n) and relative frequencies (%), median and range (minimum to maximum) or proportions (odds ratio, OR; hazard ratio, HR) with 95% confidence intervals (95% CI). Healthy volunteers were used as internal controls to define the normal range of plasma histamine levels within the study. Since D-dimer levels increase with advanced age [16], we used an age-matched cohort of healthy adults, who were recruited from a volunteer-databank at the Department of Clinical Pharmacology, Medical University of Vienna.

Between-group comparisons of continuous and categorical variables were calculated using the Mann–Whitney *U* test and the chi-square test. Predefined subgroups included patients with low molecular weight heparin (LMWH) prophylaxis and those with renal impairment. Correlations were calculated using the Spearman rank correlation test. A binominal logistic regression and a Cox proportional hazards regression analysis (with mortality as dependent variable) were applied to ascertain the effects of D-dimer and histamine on in-hospital mortality. The Box–Tidwell procedure was performed to test for linearity assumption at a significance level of $p < 0.017$. Independent variables were log transformed or inversely transformed prior to analysis according to the skewness of the distributions. The Kaplan–Meier method was used to describe survival and the log-rank test was performed to determine differences in the survival distributions according to the D-dimer level. Regarding data missing at random, only available data were analyzed. Statistical calculations were performed with SPSS Statistical Software Version 22.0 (Armonk, NY: IBM Corp). A two-tailed p-value < 0.05 was considered significant.

3. Results

Of 118 consecutive bacteremia patients screened, 72 were finally enrolled (male: 62.5%; median age: 64, range: 20–91). Remaining patients were excluded according to the predefined exclusion criteria (VKA/NOAC therapy: n = 21, recent surgical procedure: n = 10, Pitt Bacteremia Score > 2: n = 9, histamine receptor blockers/anaphylaxis: n = 4). Two patients and 1 volunteer refused to participate in the study. All included patients (100%) were followed up until hospital discharge or death. Histamine and D-dimer levels were available for 100% of cases. Bacteremia was verified by culture in 96% (n = 69) and by SeptiFast test in 4% (n = 3) of patients. The median Pitt Bacteremia Score was 1 (range: 1–2) and the median duration from blood culture sampling to the first positive culture result (time to blood culture positivity) and the subsequent period to study-related blood sampling were 11.3 h (range: 2–59) and 3.5 h (range: 1–19), respectively. All patients (100%) received antibiotic treatment upon receipt of positive blood culture result. The most frequently identified organisms were *E. coli* (n = 20, 28%) and *S. aureus* (n = 17, 24%). Table 1 shows baseline characteristics and outcome of the study cohorts and the Supplemental Figure gives the percentage distribution of bacteria causing blood stream infections.

In 14% of patients no source of infection was identified (classified as *primary bacteremia*). These patients had a higher rate of cancer (70% vs. 30%), more often immunosuppressive therapy (70% vs. 18%) and pre-existing antibiotic treatment (30% vs. 13%) and had a slightly higher rate of death (20% vs. 16%), but numbers were small in these subgroups.

Plasma histamine levels were similar between patients and healthy controls and exceeded the normal range (i.e. >10 nM) in three patients, who all had an uncomplicated course of disease. D-Dimer was elevated above normal range (>0.5 μg/mL) in 68 patients (94%). Histamine levels did not correlate with coagulation tests (fibrinogen: $r = -0.01$, prothrombin time: $r = -0.04$, D-dimer: $r = 0.04$), laboratory markers of inflammation (CRP: $r = -0.07$, leukocytes: $r = 0.12$), source of infection ($r = 0.19$), or frequency of ICU admissions ($r = 0.06$; all: $p > 0.05$). Patients with renal impairment (n = 24, 35%) had only slightly higher median histamine levels (2.4 nM, range: 1.0–8.9) than those with normal kidney function (1.4 nM, range 0–15.1; $p = 0.55$). Prophylactic anticoagulation with LMWH (40 mg enoxaparin subcutaneously daily, n = 40, 59%) was neither associated with lower histamine (2.3 nM, range: 1.0–15.1 vs. 1.1 nM, range: 0–10.8 in patients without anticoagulation; $p = 0.07$) nor with lower D-dimer values (2.1 μg/mL, range: 0.5–32 vs. 2.2 μg/mL, range: 0.3–27; $p = 0.79$).

Among all patients, in-hospital mortality occurred in 17% (n = 12). Septic shock was the documented cause of death in 83% of non-survivors (n = 10). The rate of both *S. aureus* (42% vs. 20%; $p = 0.11$) and *P. aeruginosa* infection (17% vs. 10%; $p = 0.26$) was trendwise higher in non-survivors than in survivors, while rates of *E. coli* infection (17% vs. 30%; $p = 0.70$) were lower in those who died (Table 1, Supplemental Figure). Non-survivors were older (73 vs. 60 years; $p = 0.03$)

Table 1
Baseline characteristics and outcome of study cohorts.

Variables	Volunteers (n = 36)	Survivors (n = 60)	Non-survivors (n = 12)
Age (years)	64 (27–79)	60 (20–87)	73 (43–91)
Male sex	15 (42)	40 (67)	5 (42)
Comorbid diseases			
Cancer		18 (30)	4 (33)
Solid		9 (15)	2 (17)
Hematologic		9 (15)	2 (17)
Cardiovascular disease		19 (32)	4 (33)
Diabetes mellitus		12 (20)	4 (33)
Chronic kidney disease		10 (17)	2 (17)
Liver cirrhosis		2 (3)	0
COPD		7 (12)	1 (8)
Immunosuppressive Therapy		13 (22)	2 (17)
CRP (mg/dL)	0.17 (0–0.5)	13.2 (0.5–41)	20 (5.5–31)
WBC ($\times 10^9$/L)	5.9 (4.4–10.5)	8.6 (0.01–69)	12.8 (0.04–29)
Fibrinogen (mg/dL)	325 (241–467)	604 (256–1126)	609 (191–774)
Creatinine (mg/dL)	0.9 (0.6–1.2)	1.0 (0.4–10)	1.5 (0.4–3.9)
Histamine (nmol/L)	4.3 (1–11.4)	1.7 (0–15.1)	1.8 (1–7.2)
D-dimer (μg/mL)	0.5 (0–2.8)	1.7 (0.3–6.4)	4.6 (2.8–32)
DIC score	0	2.5 (0–7)	3 (2–7)
Gram negative	n.a.	36 (60)	6 (50)
Time to blood culture positivity	n.a.	10.9 (2–59)	12.4 (3.5–31)
Source of infection[a]	n.a.		
Primary bacteremia		8 (13)	2 (17)
Urinary tract		14 (23)	1 (8)
Respiratory tract		8 (13)	3 (25)
Abdominal		10 (17)	2 (17)
Bone		3 (5)	1 (8)
Endocarditis		3 (5)	1 (8)
CVC-associated		3 (5)	1 (8)
Soft tissue infection		11 (18)	1 (8)
Staphylococcus aureus		12 (20)	5 (42)
Escherichia coli		18 (30)	2 (17)
Pseudomonas aeruginosa		6 (10)	2 (17)
Antibiotic therapy[b]	n.a.	54 (85)	10 (83)
LMWH	n.a.	34 (57)	6 (50)
Occurrence of septic shock[c]	n.a.	8 (13)	10 (83)
ICU admissions[d]	n.a.	5 (8)	9 (75)

Categorical data are presented as frequency count and percentage. Continuous variables are expressed as median and range (minimum–maximum).
Abbreviations: COPD, chronic obstructive pulmonary diseases; CRP, C-reactive protein; CVC, central venous catheter; DIC, disseminated intravascular coagulation; ICU, Intensive Care Unit; LMWH, low molecular weight heparin; WBC, white blood cell count; n.a., not applicable.
Study-related blood sampling was done 3.5 h (range: 1.0–19) after receipt of the positive blood culture result.
[a] The percentage distribution of bacteria causing blood stream infections is available with the supplement.
[b] Antibiotic therapy present at the time point of study-related blood sampling. All patients received antibiotic treatment upon receipt of positive blood culture result.
[c] Remaining two non-survivors died from multiple organ failure due to progressing underlying cancer (n = 1) and rupture of an aortic aneurysm (n = 1).
[d] One of remaining non-survivors was transferred to a palliative care clinic because of progressive incurable malignancy, and another patient suddenly died due to rupture of an aortic aneurysm. Three further patients (2 survivors and 1 non-survivor) with hematologic cancer were admitted to a specialized bone marrow transplant unit upon clinical deterioration, and one survivor with septic renal failure was temporarily treated at an intermediate care unit.

and had higher D-dimer (4.6 vs. 1.7 μg/mL; $p < 0.001$) but similar creatinine (1.5 vs. 1.0 mg/dL; $p = 0.83$) and histamine levels (1.8 vs. 1.7 nM; $p = 0.76$). There was no difference in age between patients with a D-dimer level ≥4 μg/mL and those with a D-dimer below 4 μg/mL (63 vs. 67 years; $p = 0.87$).

The time to blood culture positivity was similar between survivors and non-survivors (10.9 vs. 12.4 h; $p = 0.65$). Across all patients the time to positivity negatively correlated with D-dimer levels (rho = −0.24; $p = 0.06$); this relationship was strongest in the subgroup of patients with *E. coli* bacteremia (rho = −0.40; $p = 0.07$). No correlation was found between time to blood culture positivity and plasma histamine levels (rho = 0.04; $p = 0.76$).

Fig. 1 shows Kaplan–Meier estimates of survival stratified according to the D-dimer level.

In a binominal logistic regression analysis the odds to die increased with the D-dimer level, and was 12.6 (OR, 95% CI 3–52; $p < 0.001$; Table 2) in patients with a D-dimer ≥4 μg/mL (n = 13). The model ($\chi^2 = 23$; $p < 0.001$) correctly identified 85% of cases with a negative predictive value of 92%. In contrast to D-dimer, histamine levels were not associated with mortality (OR 0.8, 95% CI 0.3–1.9; $p = 0.6$).

Likewise, D-dimer (HR 2.5, 95% CI 1.5–4.9; $p = 0.001$) and age (HR 1.06, 95% CI 1.01–1.1; $p = 0.017$) were significantly associated with in-hospital mortality in univariable Cox regression analysis.

4. Discussion

Our study provides two major findings: (i) histamine levels are elevated only in a few patients with early bacteremia and did not predict outcome whereas (ii) increased D-dimer levels on the first day of positive blood culture are predictive of in-hospital mortality.

In contrast to our results, histamine levels in sepsis were shown to be significantly higher in non-survivors. Unfortunately this study did not provide any information on the frequency of end organ failure in the limited study population of 20 patients [5]. None of our patients had combined liver–kidney impairment, which could potentially lead to insufficient clearance of histamine levels in patients with advanced sepsis, because both organs clear histamine very efficiently [17,18]. Hence, histamine levels may only become elevated in systemic infection when multiple organ failure occurs, which may be addressed in future studies.

Although previous studies report a relationship between time to blood culture positivity and outcome [19–21], time to positivity was not associated with D-dimer levels in our study. Yet, we found a moderate negative correlation in the subgroup of patients with *E. coli* associated blood stream infection. Both the heterogeneity of bacteria causing blood stream infections and the low sample size of our study cohort may explain these findings.

Our study has two particular strengths. First, we investigated a homogenous population of non-surgical inpatients early after onset of bacteremia, but without need for intensive care at the time of enrolment. Studies on this specific population are rare compared to a vast amount of studies on septic critical illness. Secondly, blood samples were taken at a very early stage of disease — within 3.5 h after confirmation of bacteremia. This may be important because readily available parameters identifying patients with high in-hospital mortality could be of clinical relevance and may guide further hospital care. In this context, elevated D-dimer levels proved to be an early marker of mortality in early stage blood stream infection. In agreement, on-admission D-dimer levels predict disease severity and mortality in endocarditis [15] and critically ill patients [22] without overt DIC.

The main limitation of our study is that we used healthy volunteers as controls. However, we hypothesized that any kind of infection-related systemic inflammation will increase histamine release. Therefore, we did not use inpatients with infection but negative blood culture as control group. We rather decided to include only patients with clinical signs of infection with culture-proven bacteremia to investigate a homogeneous population of inpatients with ascertained bacterial infection.

Another limitation is the relatively small sample size translating into wide confidence intervals and the low mortality rate allowing only one independent variable to be included in the regression analysis, so that further studies are required to confirm the predictive value of D-dimer in this population. However, the high negative predictive value is in good agreement with the performance of D-dimer to rule out pulmonary embolism [23], and a D-dimer cut-off value of 4 μg/mL is in line with results from a study investigating the predictive value of D-dimer

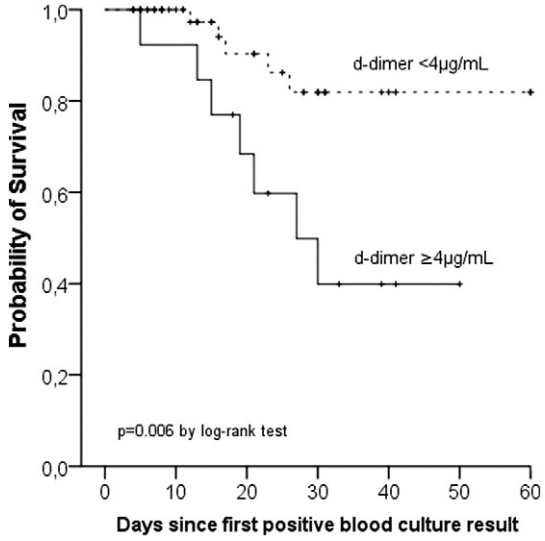

Fig. 1. Kaplan–Meier curves showing survival according to the D-dimer level. Survival estimates were 92% for patients with D-dimer <4 μg/dL and 46% for patients with D-dimer ≥4 μg/mL, respectively. Blood sampling was done on the day of first positive blood culture result.

in high-risk patients with infectious endocarditis [15] proving external validity of our findings.

5. Conclusions

We found increased histamine levels only in very few patients (4%) at an early stage of blood stream infection. In contrast, elevated D-dimer levels may be an early marker of increased mortality in non-ICU ward inpatients with culture proven bacteremia.

Learning points:

- Studies investigating inpatients with newly diagnosed bacteremia are rare compared to a vast amount of studies on septic critical illness.
- Our findings suggest that, in contrast to histamine, early-elevated D-dimer levels identify bacteremia patients at high risk for in-hospital mortality.
- D-dimer could be a promising marker of lethality in this specific population.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejim.2015.10.024.

Table 2
Univariable binominal logistic regression analysis for in-hospital mortality.

Variables	Crude OR (95% CI)	P-value
Age	**1.05** (1.01–1.10)	**0.029**
Male sex	0.36 (0.10–1.27)	0.11
CRP	1.05 (0.98–1.13)	0.17
WBC	1.03 (0.98–1.09)	0.26
Histamine	0.90 (0.67–1.20)	0.48
D-dimer ≥ 4 μg/mL	**12.6** (3.03–52.35)	**0.001**
Platelet count	1.0 (0.99–1.01)	0.73
Renal impairment	1.54 (0.43–5.49)	0.50
Time from hospitalization to first blood culture result	0.57 (0.94–1.03)	0.99
Staphylococcus aureus infection	2.86 (0.77–10.6)	0.12
Escherichia coli infection	0.47 (0.09–2.35)	0.36

95% CI, 95% confidence interval; CRP, C-reactive protein; OR, odds ratio; WBC, white blood cell count. P < 0.05 was considered significant.

Contributors

BJ conceived the study. MS, MMS, HL and NB identified eligible patients, obtained oral and written informed consent and performed study-related blood sampling. MS and BJ wrote the first draft of the manuscript and performed the statistical analysis. CS, HL, NB, PJS and TB collected data and substantially drafted the manuscript.

Conflict of interest

The authors declare no competing interests.

Acknowledgments

This work was supported by a grant from the Austrian Science Fund (SFB-54 grant: project number APF05404FW — Special Research Program: Cellular Mediators Linking Inflammation and Thrombosis, Medical University of Vienna). The Austrian Science Fund was neither involved in the conduct of the study nor in the writing of the report or in the decision to submit the article for publication.

References

[1] Gris JC, Bouvier S, Cochery-Nouvellon E, Faillie JL, Lissalde-Lavigne G, Lefrant JY. Fibrin-related markers in patients with septic shock: individual comparison of D-dimers and fibrin monomers impacts on prognosis. Thromb Haemost 2011;106:1228–30.
[2] Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. J Allergy Clin Immunol 1981;68:365–71.
[3] Neugebauer E, Rixen D, Garcia-Caballero M, Scheid B, Lorenz W. Time sequence of histamine release and formation in rat endotoxic shock. Shock 1994;1:299–306.
[4] Matsuda N, Hattori Y, Sakuraya F, Kobayashi M, Zhang XH, Kemmotsu O, et al. Hemodynamic significance of histamine synthesis and histamine H1- and H2-receptor gene expression during endotoxemia. Naunyn Schmiedebergs Arch Pharmacol 2002;366:513–21.
[5] Neugebauer E, Lorenz W, Rixen D, Stinner B, Sauer S, Dietz W. Histamine release in sepsis: a prospective, controlled, clinical study. Crit Care Med 1996;24:1670–7.
[6] Alcaniz L, Vega A, Chacon P, El Bekay R, Ventura I, Aroca R, et al. Histamine production by human neutrophils. FASEB J Off Publ Fed Am Soc Exp Biol 2013;27:2902–10.
[7] Xu X, Zhang D, Zhang H, Wolters PJ, Killeen NP, Sullivan BM, et al. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia. J Exp Med 2006;203:2907–17.
[8] Norn S, Jensen C, Dahl BT, Stahl Skov P, Baek L, Permin H, et al. Endotoxins release histamine by complement activation and potentiate bacteria-induced histamine release. Agents Actions 1986;18:149–52.
[9] Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. Allergy 2008;63:176–80.
[10] Cugno M, Cicardi M, Bottasso B, Coppola R, Paonessa R, Mannucci PM, et al. Activation of the coagulation cascade in C1-inhibitor deficiencies. Blood 1997;89:3213–8.
[11] Gardner TW, Lesher T, Khin S, Vu C, Barber AJ, Brennan Jr WA. Histamine reduces ZO-1 tight-junction protein expression in cultured retinal microvascular endothelial cells. Biochem J 1996;320(Pt 3):717–21.
[12] Steffel J, Arnet C, Akhmedov A, Iseli SM, Luscher TF, Tanner FC. Histamine differentially interacts with tumor necrosis factor-alpha and thrombin in endothelial tissue factor induction: the role of c-Jun NH2-terminal kinase. J Thromb Haemost: JTH 2006;4:2452–60.
[13] Schwameis M, Thaler J, Schober A, Schorgenhofer C, Kulinna-Cosentini C, Laggner A, et al. Tranexamic acid and fibrinogen restore clotting in vitro and in vivo in cardiac thrombus associated hyperfibrinolysis with overt bleedings. Thromb Haemost 2014;112:1071–5.
[14] Taylor Jr FB, Toh C-H, Hoots WK, Wada H, Levi M. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation, Thromb Haemost 2001;86:1327–30.
[15] Turak O, Canpolat U, Ozcan F, Yayla C, Mendi MA, Oksuz F, et al. D-dimer level predicts in-hospital mortality in patients with infective endocarditis: a prospective single-centre study. Thromb Res 2014;134:587–92.
[16] Sohne M, Kamphuisen PW, van Mierlo PJ, Buller HR. Diagnostic strategy using a modified clinical decision rule and D-dimer test to rule out pulmonary embolism in elderly in- and outpatients. Thromb Haemost 2005;94:206–10.
[17] Helander CG, Lindell SE, Westling H. The renal removal of C-14-labelled histamine from the blood in man. Scand J Clin Lab Invest 1965;17:524–8.
[18] Lindell SE, Westling H. The hepatic removal of 14C-histamine from the blood in man. Scand J Clin Lab Invest 1966;18:268–72.
[19] Khatib R, Riederer K, Saeed S, Johnson LB, Fakih MG, Sharma M, et al. Time to positivity in *Staphylococcus aureus* bacteremia: possible correlation with the source and

outcome of infection. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 41; 2005 594–8.
[20] Kim J, Gregson DB, Ross T, Laupland KB. Time to blood culture positivity in *Staphylococcus aureus* bacteremia: association with 30-day mortality. J Infect 2010;61:197–204.
[21] Willmann M, Kuebart I, Vogel W, Flesch I, Markert U, Marschal M, et al. Time to positivity as prognostic tool in patients with *Pseudomonas aeruginosa* bloodstream infection. J Infect 2013;67:416–23.
[22] Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF. D-Dimer assay predicts mortality in critically ill patients without disseminated intravascular coagulation or venous thromboembolic disease. Intensive Care Med 1999;25:207–10.
[23] Di Nisio M, Sohne M, Kamphuisen PW, Buller HR. D-Dimer test in cancer patients with suspected acute pulmonary embolism. J Thromb Haemost: JTH 2005;3:1239–42.