Regular paper

Risk stratification and prognostic value of serum neutrophil gelatinase-associated lipocalin (sNGAL) in sepsis patients

Ying Wu[1], Chen Yu[2✉], Ying Zhou[2], Zai-Ming He[1], Wei Zhang[1], Juan Fan[1] and Ying Sun[1]

[1]Department of Emergency Medicine, Liqun Hospital, Putuo District, Shanghai, China; [2]Department of Nephrology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China

Objective: Sepsis is a host response with life-threatening organ dysfunction caused by an infection. Although the overall mortality rate has increased from 30% to 37% by the surviving sepsis campaign, it is still not acceptable. Early identification, accurate stratification and appropriate intervention can improve the prognosis. In this study we assessed the risk stratification and prognostic value of serum neutrophil gelatinase-associated lipocalin (sNGAL) as a biomarker in sepsis patients. **Methods:** A total of 112 sepsis patients (38 patients with sepsis, 41 patients with severe sepsis, 33 patients with septic shock) and 25 healthy controls were enrolled in this study. Serum samples of all patients were collected and frozen before testing. Basic patient information was collected, including age, gender, primary infection, complications, and so on. Results of serum calcitonin, lactic acid, and SOFA score were followed up for 28 days. **Results:** Levels of serum procalcitonin (PCT), serum lactate, Sequential Organ Failure Assessment (SOFA) score and sNGAL of sepsis patients were significantly higher ($p<0.05$) than those of controls. The sNGAL level in sepsis patients who were alive on the 28th day of follow-up was significantly lower ($p<0.05$) than that of sepsis patients who had died before the 28th day of follow-up. Multiple logistic regression analysis showed that sNGAL-0h and lactates were independent risk factors of death due to sepsis within 28 days. At cut-off value of 250 ng/mL, the sensitivity and specificity sNGAL-0h predicting the 28-day mortality in septic patients were 0.838 and 0.827, respectively. The sNGAL level in sepsis patients with acute kidney injury (AKI) was significantly higher ($p<0.05$) than in sepsis patients without AKI. **Conclusion:** Serum NGAL may contribute to the assessment of the severity of sepsis. Serum NGAL and lactate can be independent risk factors for 28-day mortality in sepsis patients. Serum NGAL has potential of predicting septic-AKI.

INTRODUCTION

Sepsis is a kind of infection which is caused by pathogen entering blood circulation. It can progress into severe sepsis, septic shock or even multiple organ failure (Wu *et al.*, 2015). According to the statistics, 1% of patients in the hospital suffered from sepsis and 25% of patients in Intensive Care Unit (ICU) came down with sepsis (Zou *et al.*, 2014). Sepsis is one of the major causes to death of patients in the hospital, and its number reaches that of deaths due to myocardial infraction (Cecconi *et al.*, 2018). Sepsis is common in elder patients and the number of sepsis patients will increase with the aging of the population (Hall *et al.*, 2011). Early diagnosis, accurate stratification and proper intervention at an early stage of sepsis are essential in reducing its mortality (Strehlow *et al.*, 2006). Delayed diagnosis and invalid antibacterial treatment were considered as major causes of high incidence and high mortality (Balci *et al.*, 2003). Nowadays, there is no ideal biomarker that helps to diagnose or evaluate severity of sepsis in clinical practice (Wacker *et al.*, 2013). With the development and application of antibiotics, incidence and mortality of sepsis has declined but it is still not satisfying (Dellinger *et al.*, 2013a). According to the statistics, there are over 178 practical biomarkers of sepsis, small part of which are intermediates of inflammation, while most of which are anti-inflammation agents (Liu *et al.*, 2014). There is no consensus as to which kind of biomarker of sepsis is the most accurate in diagnosis and stratification (Behnes *et al.*, 2014).

Neutrophil gelatinase-associated lipocalin (NGAL), with molecular mass of 25 kDa, is a type of glycoprotein, and belongs to the lipocalin family (Devarajan, 2010; Cowland & Borregaard, 1997). NGAL is involved in immune reaction, prostaglandin synthesis and cell proliferation (Flower *et al.*, 2000). NGAL can also represent the vitality of neutrophils, which reflects a systemic infection caused by a systemic immune disease (Bosmann & Ward, 2013). NGAL can be detected both, in the blood and urine. The main source of urinary NGAL are renal tubular epithelial cells, distal to the tubules (Mori *et al.*, 2005), and serum NGAL comes not only from the damaged renal tubular system, but also from the extrarenal organs (Passov *et al.*, 2019). The difference is that the serum NGAl can reflect the body's systemic inflammatory conditions, while the urinary NGAL has a diagnostic value for acute tubular injury (Feldkamp *et al.*, 2011). Although NGAL has been proven to be an early marker for AKI, results of different studies have not reached a consensus (Zhang *et al.*, 2016).

PATIENTS AND METHOD

Patients

Basic information. According to inclusion and exclusion criteria for this study mentioned below, a total of 112 registrations in our hospital from Jul 2015 to Dec

2016 were enrolled in this study. Out of 112 patients, 58 were male and 54 were female. The average age was 71.82±8.76 years old. Basic information included age, gender, primary infection, complications (such as hypertension, diabetes, chronic lung diseases, chronic liver diseases and so on), mechanical ventilation, and hemodialysis. This study has been approved by the ethics committee of the Tongji Hospital. All patients enrolled have signed the informed consent.

Inclusion criteria. According to the "Surviving Sepsis Campaign" (Dellinger *et al.*, 2013a), age of the patients should be over 18 years old and the patient should be able to provide consent by himself/herself.

Exclusion criteria. Patients whose age was lower than 18 years old, pregnant women, malignant tumor patients, patients who suffered from the end-stage renal disease (including long-term dialysis, patients recently undergoing renal transplantation, who had had a kidney transplant before), were diagnosed and suspected to have acute radical glomerulonephritis, acute renal interstitial nephritis or renal vascular disease, were excluded from the study.

Group division. According to the diagnostic criteria for sepsis, 112 patients were divided into three subgroups: sepsis (n=38), severe sepsis (n=41) and septic shock (n=33). In the meantime, 25 healthy people who received regular health checks in our hospital were enrolled as the control group.

Sequential organ failure assessment (SOFA). The SOFA score (Lambden *et al.*, 2019) is used to evaluate dysfunction in various organ systems and when the score reaches three it is the cutoff for failure. A higher score means a number of failed organs, which suggests a severer condition and often a higher mortality. Dynamic score can reflect the evolution of the disease and treatment (see Table 1).

Statistical analysis

IBM SPSS 21.0 was used for statistical analysis. Measurement data that was in line with the normal distribution was shown as mean ±S.D. *T*-test was adapted in analyzing data from two different groups, and one-way ANOVA was adapted in analyzing data from several different groups. Non-Gauss distributed data was analyzed by a non-parametric test. The count data is expressed as a percentage and two-group data are compared using the chi-square test. Pearson analysis was adapted to assess relationship among sNGAL, PCT, level of serum lactate and SOFA score. Multiple factors logistic regression analysis was adapted to assess relationship between sepsis and age, gender, level of CRP, sNGAL, lactate, PCT and SOFA score. A significant difference was marked when *p* value is less than 0.05. *R* means coefficient of association, SE means standard error, OR means odds ratio, CI means confidence interval, and *t* value means Significance test value.

RESULTS

Basic information on sepsis patients at different stages

All of the basic information including age, gender, complications and other index values is organized in Supplementary Table 1 (at https://ojs.ptbioch.edu.pl/index.php/abp/).

Level of PCT and sNGAL, SOFA score in different subgroups of sepsis

In comparison to the level of sNGAL of Control Group that is 165.28±17.34 ng/ml, levels of sNGAL in sepsis, severe sepsis and septic shock were 215.42±29.35 ng/ml, 243.66±21.23 ng/ml, and 258.12±22.65 ng/ml, respectively, and the difference is significant ($p<0.05$). As time went by, the levels of 24-hour-sNGAL of the three subgroups were 217.82±25.66, 241.07±24.40 and 257.27±25.60, respectively, which is significantly different ($p<0.05$). Furthermore, levels of 48-hour-sNGAL of the three subgroups were 217.82±25.66, 241.07±24.40

Table 1. Sequential organ failure assessment (SOFA) score

	Index	Score				
		0	1	2	3	4
Respiration	PaO2/FiO2 (Kpa)	>53.33	40~53.33	26.67~40	13.33~26.67	<13.33
	Assisted respiration	NO	–	–	YES	–
Coagulation	Platelet ($10^9 \cdot L^{-1}$)	>150	101~150	51~100	21~50	<21
Hepatic	Bilirubin ($\mu mol \cdot L^{-1}$)	<20	20~32	33~101	102~204	>204
Circulation	Mean arterial pressure (mmHg)	≥70	<70	–	–	–
	Dose of Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0	–	≤5	5~15	>15
	Dose of Adrenaline ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0	–	–	≤0.1	>0.1
	Dose of Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0	–	–	≤0.1	>0.1
	Use of Dobutamine	NO	–	YES	–	–
Nervous	GCS score	15	13~14	10~12	6~9	<6
Renal	Serum creatinine ($\mu mol \cdot L^{-1}$)	<100	100~170	171~299	300~400	>400
	Urine volume within 24 hours (ml)	–	–	–	201~500	<200

Table 2. Relationship of sNGAL with PCT, lactate and SOFA score

	items	r	p value
sNGAL	PCT	0.394	<0.01
	Lactate	0.710	<0.01
	SOFA	0.636	<0.01

and 257.27±25.60, respectively, which is significantly different ($p<0.05$).

The r values of PCT level, lactate and the SOFA score with sNGAL in Pearson analysis were 0.394, 0.710 and 0.636, respectively (see Table 2).

Risk factors for death of sepsis within 28 days

Death of sepsis within 28 days was set as a dependent variable and age, gender, level of PCT, lactate and CRP, level of 0h-sNGAL, 24h-sNGAL and 48h-sNGAL and the SOFA score were analyzed in a logistic regression analysis. Results suggested that age, level of PCT, lactate, 0h-sNGAL, 24h-sNGAL and 48h-sNGAL, as well as the SOFA score were all risk factors for death of sepsis within 28 days (see Table 3).

In single factor logistic regression analysis, only the level of 0h-sNGAL and lactate were independent risk factors for death of sepsis within 28 days (see Supplementary Table 2 at https://ojs.ptbioch.edu.pl/index.php/abp/).

Sensitivity and specificity of sNGAL-0h and lactate predicting 28-day mortality in septic patients

When the cutoff of sNGAL-0h predicting 28-day mortality in septic patients was set as 250 ng/ml, sensitivity and specificity were 0.838 and 0.827, respectively. When the cutoff of lactate predicting 28-day mortality in septic patients was set as 6.6ng/ml, sensitivity and specificity were 0.892 and 0.653, respectively. Area under curve (AUC) of ROC curve of sNGAL-0h was less than that of lactate, so the specificity of sNGAL-0h was better (see Table 4).

Level of PCT, lactate, sNGAL and SOFA score in AKI patients

Levels of PCT, lactate and creatine in the serum and SOFA score in sepsis without AKI patients were not significantly different from those of sepsis with AKI patients. However, the level of 0h-sNGAL in sepsis without AKI patients (217.48±27.08) was lower than that of

Table 3. Single factor logistic regression analysis

Item	B	SE	Wals	p	OR (95%CI)
age	0.149	0.035	17.965	<0.01	1.161 (1.083 ~ 1.243)
gender	−0.136	0.403	0.114	0.736	0.873 (0.396 ~ 1.922)
Oh-sNGAL	0.069	0.014	25.875	<0.01	1.072 (1.043 ~ 1.101)
24h-sNGAL	0.079	0.014	30.916	<0.01	1.082 (1.052 ~ 1.112)
48h-sNGAL	0.082	0.014	32.016	<0.01	1.085 (1.055 ~ 1.116)
PCT	0.070	0.019	13.302	<0.01	1.073 (1.033 ~ 1.114)
lactate	0.650	0.125	4.400	<0.01	1.915 (0.499 ~ 2.447)
SOFA	0.665	0.134	24.639	<0.01	1.944 (1.495 ~ 2.527)
CRP	0.020	0.010	4.380	0.304	1.009 (0.992 ~ 1.027)

B is one coefficient; Wals is one statistical magnitude.

Table 4. Sensitivity and specificity of sNGAL-0h and lactate predicting 28-day mortality in septic patients

Items	AUC-ROC	p	Cutoff	Sensitivity	Specificity	CI (95%)
sNGALOh	0.873	<0.05	250	0.838	0.827	(0.800 ~ 0.946)
lactate	0.899	<0.05	6.6	0.892	0.653	(0.842 ~ 0.957)

Table 5. Levels of creatine, sNGAL, PCT and lactate, and SOFA score in sepsis with(out) AKI patients

Items	Sepsis without AKI	Sepsis with AKI	t	p
	n=46	n=11		
Creatine				
0h (umol/l)	88.71±18.13	88.68±18.22	−0.004	0.997
48h (umol/l)	82.21±11.31	150.18±23.41	−9.369	0.000
sNGAL				
0h (ng/ml)	217.48±27.08	245.09±26.03	−3.060	0.007
24h (ng/ml)	219.00±25.66	243.91±24.65	−2.987	0.009
48h (ng/ml)	222.70±22.16	259.00±24.36	−4.516	0.000
PCT (ng/ml)	12.00±5.68	12.36±5.55	0.194	0.849
Lactate (mmol/l)	4.33±2.38	6.05±3.61	−1.499	0.159
SOFA score	5.02±1.75	5.82±2.48	−1.249	0.217

sepsis with AKI patients (245.09±26.03), which is significantly different ($p<0.05$). As the disease developed, the level of 24h-sNGAL and 48h-sNGAL in sepsis without AKI patients (219.00±25.66 and 222.70±22.16) was still lower than that of sepsis with AKI patients (243.91±24.65 and 259.00±24.36), which is significantly different ($p<0.05$) (see Table 5).

DISCUSSION

Sepsis, particularly severe sepsis, septic shock and sepsis accompanied by organ failure, has become a major problem in patients in the hospital and their number reaches a million all over the world (Dombrovskiy et al., 2007; Vincent et al., 2009). Some studies have found that dysfunction of organs or cognition of those patients who survived sepsis were considered as a factor that doubled the risk of death during hospitalization within 5 years (Iwashyna et al., 2010; Quartin et al., 1997). Consequently, sepsis and its complications have always been a major public health problem which brings a burden onto the whole society (Moss, 2005). Someone even took sepsis as a hidden disaster of public sanitation (Angus, 2010). In 1980, the initial focus on sepsis was the early stage of inflammation and TNFα, IL1β and IL6 were considered to start SIRS. CRP, a group of proteins increasing in the liver by IL6 synthesis, was used as a potential biomarker. At that time, a large dose of glucocorticoids in the regimen was used to treat sepsis (Vandewalle & Libert, 2020). In 1990, researchers found that PCT levels were elevated in patients with bacterial infections and PCT was then considered as another potential biomarker (Karzai et al., 1997). PCT and CRP can assist in the diagnosis and staging of sepsis, and PCT is a relatively new biomarker but relevant to systemic inflammation, infection and sepsis (Assicot et al., 1993). In comparison to CRP, PCT shows better specificity and is more closely related to prognosis (Cai et al., 2010, Hur et al., 2009). Therefore PCT is now widely used as a biomarker in clinical practice. However, predicting value of PCT is doubtable because of lack of evidence (Karlsson et al., 2010; Kibe et al., 2011). Although no single biomarker proved to be ideal for sepsis over the past three decades, there are at least some biomarkers that can identify critically ill patients, making it possible to provide early diagnose, early treatment, and improved prognosis (Dellinger et al., 2013b).

In all 112 cases enrolled in our study, we checked the level of PCT, lactate and sNGAL, as well as the SOFA score in different groups. The results showed an elevated level of PCT in sepsis patients which suggested an infection by bacteria (Assicot et al., 1993). We also found that as disease has severely progressed, the PCT level increased and the levels of lactate and sNGAl had a similar tendency. Similar results were found in the Haasefielitz and others study (Haasefielitz et al., 2014). Therefore, we can conclude that sNGAL could be used in the risk stratification of sepsis (Wang et al., 2014). Bacterial infection and dysfunction of several organs caused by infection account for that level of sNGAL which increased as the disease developed. Referring to former studies about PCT (Becker et al., 2008; Billeter et al., 2009), we could not set a cutoff for sNGAL in diagnosis of sepsis.

In this study, results suggested that an increased mortality could be related to aging (Hall et al., 2011), accompanied by AKI (Wheeler et al., 2008) and septic shock (Yan et al., 2001). We found that age, level of PCT, lactate, 0h-sNGAL, 24hsNGAL and 48h-sNGAL, as well as the SOFA score were all risk factors for death due to sepsis within 28 days, but only the levels of 0h-sNGAL and lactate were independent risk factors for death of sepsis within 28 days. Similar results were found in the Mikkelsen and others study (Mikkelsen et al., 2009). The levels of 0h-sNGAL and lactate can be used to predict death of sepsis within 28 days and 0h-sNGAL has a higher specificity than lactate.

In comparison to creatine, sNGAL has more value in diagnosis of AKI and similar results were found in the Bagshaw and others study (Bagshaw et al., 2010). In the Hong and others study (Nga et al., 2015), 48-h sNGAL has more value in predicting AKI and similar result was also found in our study.

This study is a single center observation which has a bias during sample collection. The number of sepsis patient cases is not abundant and equivalent among groups.

In summary, sNGAL could be used in risk stratification and prognosis in sepsis patients. The levels of sNGAL and lactate could be single risk factors for death of sepsis within 28 days. In comparison to creatine, 48h-sNGAL has more value in predicting AKI in sepsis patients. However, more studies are needed to provide deeper evidence for these methods.

REFERENCE

Angus DC (2010) The lingering consequences of sepsis: a hidden public health disaster? *JAMA* **304**: 1833–1834. https://doi.org/10.1001/jama.2010.1546

Assicot M, Bohuon C, Gendrel D, Raymond J, Carsin H, Guilbaud J (1993) High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* **341**: 515–518. https://doi.org/10.1016/0140-6736(93)90277-N

Bagshaw SM, Haase BM, Fielitz AH, Egi M, Morimatsu H, D'amico G, Goldsmith D, Devarajan P, Bellomo R (2010). Plasma and urine neutrophil gelatinase-associated lipocalin in septic *versus* non-septic acute kidney injury in critical illness. *Int Care Med* **36**: 452–461. https://doi.org/10.1007/s00134-009-1724-9

Balci C, Sungurtekin H, Gürses E, Sungurtekin U, Kaptanoglu B (2003) Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. *Critical Care* **7**: 85. https://doi.org/10.1186/cc1843

Becker KL, Snider R, Nylen ES (2008) Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med* **36**: 941. https://doi.org/10.1097/CCM.0B013E318165BABB

Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, Borggrefe M, Hoffmann U (2014) Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. *Crit Care* **18**: 507. https://doi.org/10.1186/s13054-014-0507-z

Billeter A, Turina M, Seifert B, Mica L, Stocker R, Keel M (2009) Early serum procalcitonin, interleukin-6, and 24-hour lactate clearance: useful indicators of septic infections in severely traumatized patients. *World J Surg* **33**: 558–566. https://doi.org/10.1007/s00268-008-9896-y

Bosmann M, Ward PA (2013) The inflammatory response in sepsis. *Trends Immunol* **34**: 129–136. https://doi.org/10.1016/j.it.2012.09.004

Cai L, Rubin J, Han W, Venge P, Xu S (2010) The origin of multiple molecular forms in urine of HNL/NGAL. *Clin J Am Soc Nephrol* **5**: 2229–2235. https://doi.org/10.2215/CJN.00980110

Cecconi M, Evans L, Levy M, Rhodes A (2018) Sepsis and septic shock. *Lancet* **392**: 75–87. https://doi.org/10.1016/s0140-6736(18)30696-2

Cowland JB, Borregaard N (1997) Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. *Genomics* **45**: 17. https://doi.org/10.1006/geno.1997.4896

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee Including the Pediatric S (2013a) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Int Care Med* **39**: 165–228. https://doi.org/10.1007/s00134-012-2769-8

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee Including the Pediatric S (2013b) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* **41**: 580–637. https://doi.org/10.1097/CCM.0b013e31827e83af

Devarajan P (2010) Review: neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury. *Nephrology* **15**: 419–428. https://doi.org/10.1111/j.1440-1797.2010.01317.x

Dombrovskiy V Y, Martin A A, Sunderram J, Paz H L (2007) Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* **35**: 1244–1250. https://doi.org/10.1097/01.CCM.0000261890.41311.E9

Feldkamp T, Bienholz A, Kribben A (2011) Urinary neutrophil gelatinase-associated lipocalin (NGAL) for the detection of acute kidney injury after orthotopic liver transplantation. *Nephrol Dialys Transplant* **26**: 1456–1458. https://doi.org/10.1093/ndt/gfr146

Flower DR, North AC, Sansom CE (2000) The lipocalin protein family: structural and sequence overview. *Biochim Biophys Acta* **1482**: 9–24. https://doi.org/10.1016/s0167-4838(00)00148-5

Haasefielitz A, Haase M, Devarajan P (2014) Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. *Ann Clin Biochem* **51**: 335–351. https://doi.org/10.1177/0004563214521795

Hall MJ, Williams SN, Defrances CJ, Golosinskiy A (2011) Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *Nchs Data Brief* **62**: 1

Hur M, Moon HW, Yun YM, Kim KH, Kim HS, Lee KM (2009) Comparison of diagnostic utility between procalcitonin and C-reactive protein for the patients with blood culture-positive sepsis. *Korean J Lab Med* **29**: 529. https://doi.org/10.3343/kjlm.2009.29.6.529 (in Korean)

Iwashyna TJ, Ely EW, Smith DM, Langa KM (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* **304**: 1787. https://doi.org/10.1001/jama.2010.1553

Karlsson S, Heikkinen M, Pettilä V, Alila S, Väisänen S, Pulkki K, Kolho E, Ruokonen E, Group FS (2010) Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study. *Crit Care* **14**: R205. https://doi.org/10.1016/j.medin.2011.09.008

Karzai MW, Oberhoffer MM, Meierhellmann MA, Reinhart MK (1997) Procalcitonin – A new indicator of the systemic response to severe infections. *Infection* **25**: 329–334. https://doi.org/10.1007/BF01740811

Kibe S, Adams K, Barlow G (2011) Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemotherap* **66** (Suppl 2): ii33. https://doi.org/10.1093/jac/dkq523

Lambden S, Laterre PF, Levy MM, Francois B (2019) The SOFA score-development, utility and challenges of accurate assessment in clinical trials. *Crit Care* **23**: 374. https://doi.org/10.1186/s13054-019-2663-7

Liu T, Chen HW, Liang DY, Hou YQ (2014) Progressof prognostic markers in sepsis. *Int J Lab Med* **35**: 2794–2796

Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, Bellamy SL, Christie JD (2009) Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* **37**: 1670–1677. https://doi.org/10.1097/CCM.0b013e31819fcf68

Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidtott KM, Chen X, Li JY, Weiss S (2005) Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* **115**: 610–621. https://doi.org/10.1172/JCI23056

Moss M (2005) Epidemiology of sepsis: race, sex, and chronic alcohol abuse. *Clin Infect Dis* **41** (Suppl 7): S490. https://doi.org/10.1086/432003

Nga HS, Medeiros P, Menezes P, Bridi R, Balbi A, Ponce D (2015) Sepsis and AKI in clinical emergency room patients: The role of urinary NGAL. *Biomed Res Int* **2015**: 413751. https://doi.org/10.1155/2015/413751

Passov A, Petäjä L, Pihlajoki M, Salminen US, Suojaranta R, Vento A, Andersson S, Pettilä V, Schramko A, Pesonen E (2019) The origin of plasma neutrophil gelatinase-associated lipocalin in cardiac surgery. *BMC Nephrol* **20**: 182. https://doi.org/10.1186/s12882-019-1380-4

Quartin AA, Schein RMH, Kett DH, Peduzzi PN (1997) Magnitude and duration of the effect of sepsis on survival. *JAMA* **277**: 1058

Strehlow MC, Emond SD, Shapiro NI, Pelletier AJ, Jr CC (2006) National study of emergency department visits for sepsis, 1992 to 2001. *Ann Emerg Med* **48**: 326–331. https://doi.org/10.1016/j.annemergmed.2006.05.003

Vandewalle J, Libert C (2020) Glucocorticoids in sepsis: To be or not to be. *Front Immunol* **11**: 1318. https://doi.org/10.3389/fimmu.2020.01318

Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y (2009) International study of the prevalence and outcomes of infection in intensive care units. *JAMA* **302**: 2323. https://doi.org/10.1001/jama.2009.1754

Wacker C, Prkno A, Brunkhorst FM, Schlattmann P (2013) Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infectious Dis* **13**: 426–435. https://doi.org/10.1016/S1473-3099(12)70323-7

Wang M, Qian Z, Xin Z, Dong G, Li C (2014) Diagnostic and prognostic value of neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-9, and tissue inhibitor of matrix metalloproteinases-1 for sepsis in the Emergency Department: an observational study. *Crit Care* **18**: 634. https://doi.org/10.1186/s13054-014-0634-6

Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, Wong HR (2008) Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically Ill children with septic shock. *Crit Care Med* **36**: 1297. https://doi.org/10.1007/s00134-020-06106-2

Wu J, Hu L, Zhang G, Wu F, He T (2015) Accuracy of presepsin in sepsis diagnosis: A systematic review and meta-analysis. *Plos One* **10**: e0133057. https://doi.org/10.1371/journal.pone.0133057

Yan L, Borregaard N, Kjeldsen L, Moses MA (2001) The high molecular weight urinary matrix metalloproteinase (MMP) activity is a complex of gelatinase B/MMP-9 and neutrophil gelatinase-associated lipocalin (NGAL) modulation of MMP-9 activity by NGAL. *J Biol Chem* **276**: 37258–37265. https://doi.org/10.1074/jbc.M106089200

Zhang A, Cai Y, Wang PF, Qu JN, Luo ZC, Chen XD, Huang B, Liu Y, Huang WQ, Wu J (2016) Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis. *Crit Care* **20**: 41. https://doi.org/10.1186/s13054-016-1212-x

Zou Q, Wen W, Zhang XC (2014) Presepsin as a novel sepsis biomarker. *World J Emerg Med* **5**: 16. https://doi.org/10.5847/wjem.j.issn.1920-8642.2014.01.002