A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity

Chamindie Punyadeera, E Marion Schneider, Dave Schaffer, Hsin-Yun Hsu, Thomas O Joos, Fabian Kriebel, Manfred Weiss, Wim FJ Verhaegh

1 Department of Molecular Diagnostics, Philips Research, High Tech Campus 12a, 5656 AE Eindhoven, Netherlands
2 Experimental Anesthesiology, University Hospital Ulm, Steinhoevelstr. 9, 89075 Ulm, Germany
3 Philips Research North America, 345 Scarborough Road, Briarcliff Manor, NY 10510, USA
4 Natural and Medical Sciences Institute, University of Tuebingen, Markwiesenstr. 55, 72770 Reutlingen, Germany
5 Clinical Anesthesiology, University Hospital Ulm, Steinhoevelstr. 9, 89075 Ulm, Germany

Click here for correspondence address and email

Date of Submission 26-Jan-2009
Date of Acceptance 18-May-2009
Date of Web Publication 5-Jan-2010

Abstract

Introduction: In this study, we report on initial efforts to discover putative biomarkers for differential diagnosis of a systemic inflammatory response syndrome (SIRS) versus sepsis; and different stages of sepsis. In addition, we also investigated whether there are proteins that can discriminate between patients who survived sepsis from those who did not. Materials and Methods: Our study group consisted of 16 patients, of which 6 died and 10 survived. We daily measured 28 plasma proteins, for the whole stay of the patients in the ICU. Results: We observed that metalloproteinases and sE-selectin play a role in the distinction between SIRS and sepsis, and that IL-1α, IP-10, sTNF-R2 and sFas appear to be indicative for the progression from sepsis to septic shock. A combined measurement of MMP-3, IL-1α, IP-10, sIL-2R, sFas, sTNF-R1, sRAGE, GM-CSF, IL-1β and Eotaxin allows for a good separation of patients that survived from those that died (mortality prediction with a sensitivity of 79% and specificity of 86%). Correlation analysis suggests a novel interaction between IL-1α and IP-10.

Conclusion: The marker panel is ready to be verified in a validation study with or without therapeutic intervention

Keywords: Biomarker, cellular mechanism, sepsis outcome, SIRS, sepsis stage

How to cite this article:
Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaegh WF. A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity. J Emerg Trauma Shock 2010;3:26-35

How to cite this URL:
Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaegh WF. A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity. J Emerg Trauma Shock [serial online] 2010 [cited 2014 Oct 21];3:26-35. Available from: http://www.onlinejets.org/text.asp?2010/3/1/26/58666
A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity

Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaegh ...

A consensus conference in 1992 first published agreed-upon definitions of systemic inflammatory response syndrome (SIRS), sepsis (SIRS with known or suspected infection), severe sepsis and septic shock. With these operational definitions in hand, statistics on incidents have been collected and have established that sepsis is the tenth leading cause of death in the USA with over 700 000 cases a year and with mortality rates above 30%. The incidents continue to increase, with unacceptably high mortality rates, despite the use of a wide variety of therapies and continuing research.

During the onset of sepsis, a massive inflammatory reaction occurs in the initial phase, which is followed by a variable anti-inflammatory response. These events involve chemical mediators, such as cytokines and chemokines, and inflammatory cells, such as the polymorphonuclear neutrophils and macrophages. Therefore, inflammatory as well as anti-inflammatory biomarkers could potentially be used for diagnosis and outcome prediction. Moreover, such biomarkers may stimulate evidence-based medicine, the design of preventive clinical approaches as well as personalized treatment protocols. As our first effort in this direction, we analyzed a dataset consisting of 28 plasma proteins collected from patients during their stay in an intensive care unit (ICU). The following clinically relevant aspects were addressed:

- differential diagnosis of SIRS versus sepsis;
- sepsis disease severity and
- the outcome (survival or death due to sepsis).

In this study, we demonstrate the relevance of MMP-1, -2, -7, -13 and sE-selectin for the distinction between SIRS and sepsis. The down modulation of MMPs may be relevant to facilitate receptor re-expression, which was impaired in an infection-independent systemic inflammation (SIRS). Further, we identified a set of biomarkers related to sepsis disease severity. These were IL-10 related to apoptosis and inflammation, IP-10 related to leukocyte recruitment into inflamed organs and sTNF-R2 and sFas related to a pro-inflammatory environment with little beneficial effect on functional modulation of the sepsis scenario.

Materials and Methods

Patient population

Sixteen ICU patients were included in this prospective study and recorded daily over 4-15 days. All patients were surgical patients: polytraumatized, after abdominal, lung and great vessel surgery. From admission to ICU to discharge from the ICU, we aggregated clinical data into the following scores:

- SAPS II (Simplified Acute Physiological Score II): 17 variables (12 physiological variables, age, admission for medical or scheduled/unscheduled surgery and underlying diagnosis (acquired immunodeficiency syndrome, metastatic cancer, hematologic malignancy)).
- SOFA (Sequential Organ Failure Assessment) score: status of six organ systems (respiration, coagulation, liver, cardiovascular, central nervous system, renal).
- Sepsis score: graded, based on the international sepsis definitions, as: (1) local infection, (2) bacteremia, (3) SIRS, (4) sepsis, (5) severe sepsis, (6) septic shock.

Sepsis was defined using the original 1992 ACCP/SCCM sepsis definitions. In the present study, due to the 1992 definitions, a systemic inflammatory response syndrome (SIRS) was manifested in patients by two or more of the four conditions: temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or PaCO₂ <32 torr and white blood cell count (WBC) >12 000 cells/mm³ or <4000 cells/mm³. If SIRS was due to a documented infection, patients were classified as sepsis patients. Severe sepsis was defined as sepsis plus organ dysfunction. Septic shock was defined as severe sepsis plus shock. Severity of sepsis is proposed to increase firstly by association with organ dysfunctions and secondly by additional shock. As recommended, in the present study, applying the 1992 sepsis definitions, organ failure was regarded to be present if patients had lactic acidosis or oliguria, or reached greater than two points in one organ system (lung, coagulation, liver, kidney) using the SOFA score. Greater than two points are reached in the SOFA score for the organ system lung with PaO₂/FiO₂ ≤200 with respiratory support, for coagulation with platelets ≤50 000/μl, for liver with bilirubin >6 mg/dl or 102 μmol/l, for kidney with creatinine >3.5 mg/dl or >300 μmol/l or with urine output <500 ml/day. Septic shock was defined as hypotension despite adequate volume resuscitation, a systolic blood pressure of ≤90 mmHg or the need of vasopressors to keep blood pressure >90 mmHg.

In total, 118 samples were collected from the abovementioned 16 patients. Six of these patients died, and 10 survived. In addition to these 16 patients, four healthy volunteers of the same age without SIRS or sepsis were included in the study, each contributing one plasma sample.
In the plasma samples, 28 biomolecules were analysed using the Luminex system (USA): 10 cytokines (TNF-α, IL-1β, Eotaxin, IL-13, MIP-1α, IL-10, IL-1β, IP-10, GM-CSF and IFN-γ), 8 matrix metalloproteinases (MMP-1, -2, -3, -7, -8, -9, -10 and -13) and 10 soluble factors (GP130, IL-2R, ICAM, E-selectin, Fas, TNF-R1, TNF-R2, RAGE, VCAM and MIF). The inter- and intra-assay variation was <10% (data not shown).

The choice for the abovementioned biomolecules is motivated as follows. Inflammation caused by tissue damage (SIRS) is primarily mediated by activation of the inflammasome - consecutively raising IL-1β, TNF-α in the tissue. Theses cytokines cause the release of soluble TNF-receptors. In the plasma, soluble TNF-R2 appears to be more sensitive than sTNF-R1. In the infection-associated inflammation, TLR activation may be responsible for the induction of IFN-γ, as well as NF-kB-guided cytokines such as TNF-α, IL-8, IL-6, etc. some of which may be rapidly bound by receptors and are sensitive to detection assays using two monoclonal antibodies such as multiplexed bead associated assays. Generally, inflammation causes activation of many proteases and metalloproteases, which are either beneficial by degrading matrix proteins or are detrimental by cleaving receptors and contribute to anergy and non-responsiveness that appears to be a key factor in sepsis-associated pathogenesis. Finally, we chose soluble receptors to be determined since these biomarkers indicate which receptors are regulated in a defined disease state. Soluble ICAM, for instance, indicates whether transendothelial migration is one of the major processes going on at a defined time point. In a third aspect, we questioned the contribution of macrophages in the inflammatory process. Monocytes often disappear from the peripheral leukocyte population in patients with major SIRS or sepsis and we believe that they go to tissues. We chose MIP-1α to assess functional macrophage activity.

Analysis methods

ANOVA analysis

We performed an ANOVA on each biomolecule to discover differences among the four disease codes (3-SIRS, 4-sepsis, 5-severe sepsis, 6-septic shock). The distributions of measured values were not close to a normal distribution (assumed by ANOVA), so the data were log transformed before analysis. The numbers of observations available varied due to different lengths of the patients’ stay at the ICU. As shown in [Table 1], some patients have many observation days with septic shock (such as patients #8 and #10), whereas others have observation days with SIRS only (patient #9). Four patients (#2, #5, #11 and #14) had days with SIRS and days with some form of sepsis, with patients #2, #5 and #14 first having some form of sepsis, and later have SIRS, and patient #11 starts with SIRS, which later turned into severe sepsis, and had SIRS again on the last day. Note that a patient can go from sepsis to SIRS if (s)he is successfully treated, as then microorganisms and infection may no longer be proven and hence the sepsis criteria are no longer met, while the criteria for SIRS can still be fulfilled.

Unfortunately, no design could be found that permitted the rigorous separation of the patient and day effects. We therefore treated each observation as independent, but adjusted the degrees of freedom of the F test to correct for these effects. Bonferroni correction was used to correct for the multiple tests, as we test 28 biomolecules simultaneously.

Correlation analysis

Next, as a second step we performed a correlation analysis and computed the Pearson correlation between the log-transformed measurements of each of the biomolecules on the one hand, and each of the following eight labels on the other:

- SIRS (code 3) versus sepsis (code 4);
- SIRS (code 3) versus sepsis, severe sepsis and septic shock (codes 4, 5, 6);
- sepsis (code 4) versus severe sepsis and septic shock (codes 5, 6);
- sepsis (code 4) versus septic shock (code 6);
- sepsis (code 4) versus severe sepsis (code 5);
- the SOFA score;
- the SAPS II score and
- the outcome (survival/death).

As a reference, to determine the significance level for each of the computed correlations, we determined what correlations can be obtained by chance, by randomly permuting each label 10 000 times and computing the correlation to each of the biomolecules. In this way, we obtained expected correlations and variances, which we used to compute P-values. In addition, we again applied the Bonferroni-correction for multiple testing. Note again that the obtained P-values are biased, as we treated each sample as independent, whereas these come from a limited number of patients.

Pattern recognition analysis

In a third step, we performed a search for combinations of biomolecules that could give rise to a classifier to distinguish SIRS (code 3) from the septic condition (code 4). The idea was to see if a diagnostic biomarker set might be identified to distinguish sepsis from SIRS conditions.

For this, a genetic algorithm [6] especially devised for subset selection was used. To identify small subsets of these biomolecules that would make the desired distinction, a support vector machine was trained on some of the observations and then tested on others. Because of missing data issues, six biomolecules were discarded (MMP-3, -7, IL-13, IFN-γ, sE-selectin and sVCAM). The final learning set consisted of 34 observations, 20 in SIRS and 14 in sepsis, from 10 patients among whom only patient #2 contributed observations to both conditions (see [Table 1]). Because of the stochastic nature of both the genetic search and the training of candidates on differing sets of observations, 10 independent searches were performed. Approximately two-thirds of the available observations were used for training and all were used for testing.
Prediction SIRS versus sepsis and predicting outcome

In a fourth step, we developed rules for predicting SIRS versus sepsis and for predicting mortality, and we generated the corresponding receiver operating characteristic (ROC) curves.

For predicting SIRS (code 3) versus sepsis (code 4), we took the individual biomolecules that we identified in the previous two steps, and simply used a threshold rule, i.e. above a certain threshold the patient's sample is classified as sepsis, and below it the sample is classified as SIRS. By varying the threshold, we created an ROC curve.

For predicting mortality, we applied a naïve Bayesian classifier, using the panel of biomolecules that were identified to correlate significantly to the outcome. We applied a leave-one-out scheme, i.e., the classification of each sample is done by a classifier that is trained on the set of samples not including the particular sample at hand. By varying the classification threshold on the posterior probability, we again created an ROC curve. We also calculated sensitivity and specificity for the default threshold level and plotted the correctness of mortality prediction for the different patients and for their different days during the ICU stay. When making mortality predictions for new samples, the Bayesian classifier can be trained on all samples from this study, and directly applied to the measurements of the new samples.

Correlations between biomolecules

The final analysis was to compute the Pearson correlation between the log measurements for each pair of biomolecules.

Results and Discussion

Results of the experiments

ANOVA analysis

The results of the ANOVA showed that MMP-1, -2, -7, -13 and sE-selectin are significantly lower in septic cases than in SIRS cases. Furthermore, IP-10, sFas and sTNF-R2 were elevated most in the plasma of patients in septic shock. Corresponding P-values after Bonferroni correction are below 0.01. We have to note, though, that these results may still contain the confounding of patients with sepsis state (see discussion). [Figure 1] and [Figure 2] show the ranges of the log measurements for the above-described biomolecules.

Correlation analysis

The correlation analysis resulted in the following findings.

- MMP-1, -2, -7 and -13 plasma concentrations showed to be significantly lower (P < 0.001) in sepsis (code = 4) as compared to SIRS (code = 3), with absolute correlation values ~0.8.
- In addition to these four, IL-1α, IP-10 and sTNF-R2 were higher (P < 0.05) in sepsis, severe sepsis and septic shock (codes = 4, 5, 6) as compared to SIRS (code = 3).
- sFas and sTNF-R2 were higher (P < 0.05) in severe sepsis and septic shock (codes = 5, 6) as compared to sepsis (code = 4) and also in septic shock (code = 6) as compared to sepsis (code = 4).
- MMP-2, MMP-7 and IL-1β were negatively correlated to the SAPS II score (P < 0.01) and MMP-3, IL-1α, IP-10, sFas, sTNF-R1 and sTNF-R2 were positively correlated to the SAPS II score (P < 0.001). The correlation of sTNF-R1 was relatively high (0.78).
- Many biomolecules were correlated with the SOFA score (P < 0.01), with however slightly lower absolute correlations (up to 0.50). MMP-2, -7, IL-1β, Eotaxin, GM-CSF and IFN-γ were negatively correlated, and MMP-3, -8, -10, IL-10, IP-10, sFas, sTNF-R1 and sTNF-R2 were positively correlated.
- The patients who died from septic complications had elevated levels of MMP-3, -10, IL-1α, IP-10, sIL-2R, sFas, sTNF-R1, sTNF-R2 and sRAGE as compared to the surviving patients (P < 0.05). In contrast, the former patients showed low levels of GM-CSF, IL-1β and Eotaxin (P < 0.05).

Pattern recognition analysis

[Table 2] shows the set of best-performing classifiers. Each line in the table gives a biomarker set (consisting of two or three biomolecules), and the associated performance in terms of average number of errors over the 10 independent runs, and the maximum error over the 10 runs.

We note that in no case did any of these classifiers make an average (over the 10 runs) worse than 2 errors out of a possible 34. We see the MMPs are strongly being represented. Half of the errors are contributed by measurements of patient #11 on day 8, while the other half is contributed by patient #2, the only patient contributing measurements to both the SIRS and sepsis classes. This may be an indication of the possible confounding of patient effects with the clinical distinction we are seeking.

[Table 2] indicates three strong pairs of compounds: MMP-2 with MMP-8, MMP-8 with MMP-13 and MMP-13 with MIP-1α (although this pair did not meet our error cutoff without adding a third biomolecule). The role of MIP-1α and MMP-8 is quite striking, as they are in themselves hardly indicative for being SIRS (code 3) or sepsis (code 4); the correlation analysis indicated that their correlations to that label are quite...
A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaegh ...

Prediction SIRS versus sepsis and predicting outcome

The ROC curves are shown in Figure 4. We see that SIRS can be distinguished from sepsis by using MMP-1, -2, -7, or -13 with an AUC of more than 0.95 ($P < 2e-6$). E-selectin performs a bit worse, with an AUC of 0.80 ($P < 0.005$). For predicting mortality, we see that by using the panel of biomolecules identified by the correlation analysis, consisting of MMP-3, -10, IL-1β, IP-10, sIL-2R, sFas, sTNF-R1, sTNF-R2, sRAGE, GM-CSF, IL-1β and Eotaxin, we get a much higher AUC (0.89, $P = 3.6e-13$) than by using the SAPS II or SOFA score.

Figure 5 shows the correctness of the mortality prediction for all patients and all their days during his/her ICU stay. We observe that the predictions are already accurate during the first two days for 12 of the 16 patients (although patient #5 has no measurement on day two), two patients (#4 and #10) have a wrong prediction on one of the first two days, and two patients (#13 and #15) have wrong predictions on their both first days. This means that the classifier can be used as an early predictor of mortality. Counting the overall samples, we have 33 true positive and 9 false negative predictions, giving a sensitivity of 79%. Furthermore, we have 65 true negative and 11 false positive predictions, giving a specificity of 86%.

Correlations between biomolecules

The Pearson correlation between the log measurements for each pair of biomolecules is depicted in Figure 6. Three groups of strongly correlating biomarker concentrations appear in the figure:

- MMP-1, MMP-2, MMP-7 and MMP-13;
- TNF-α, IL-1β, Eotaxin, IL-13 and GM-CSF and
- IL-1α and IP-10.

Biological interpretation

MMPs and sE-selectin

When we combined biomolecules that could give rise to a better distinction of SIRS and sepsis, using a genetic algorithm devised for subset selection, we found the following remarkable biomarker pairs: MMP-13 with MMP-1α (not alone, but combined with either sFas, sGP-130, sICAM, sIL-2R, sRAGE or sTNF-R2), MMP-2 with MMP-8 and MMP-8 with MMP-13. All of these are related to tissue remodelling and leukocyte chemotaxis and recruitment. MMP-2 and -13 are also best classifiers for SIRS and sepsis as demonstrated in the biplot in Figure 3 and the ROC curves in Figure 4. Correlation analysis Figure 6 shows that MMP-1, -2, -7 and -13 strongly correlate. Out of the inflammatory cytokine panel IL-1β and TNF-α correlated, which supports the observation that TNF-α is a major inducer of IL-1β in sepsis, which has been known for a long time. Eotaxin, IL-13 and GM-CSF may play a role in concomitant recruitment of TH2 lymphocytes and myeloid progenitors including eosinophils, respectively. The correlation of IL-1α and IP-10 detected here is indeed challenging since the chemokine IP-10 is dependent on Interferon-activation and IL-1α is a member of the highly promiscuous cytokine family related to NF-κB activation. The biomarkers identified are interesting because of arguments based on clinical observations but also based on basic science.

In this study, we provide evidence for a high discriminative value of defined MMPs between SIRS (code = 3) and sepsis (code = 4). Following Figure 1 and the ANOVA and correlation analyses, MMP-1, -2, -7, -13 and sE-selectin are higher in SIRS as compared to sepsis. MMP-7 remains low in all stages of sepsis including septic shock. This MMP-7 was found to be significantly lower in patients with an NQO-1 mutation suggesting that MMP-7 diminution may be related to oxidative stress (Schneider et al., unpublished data). Matrix metalloproteinases are involved in extracellular matrix remodeling and cell migration that occur following injury or infections. MMP-7 mediates cleavage of E-cadherin to stimulate transmigrational movement of neutrophils controlling bacterial infections. Studies in mice suggest that MMP-7 also regulates the antimicrobial activity of defensins in intestinal mucosa. Moreover, MMP-7, the matrilysin cleaves a number of nonstructural proteins, such as pro-TNF-α and Fas-L, and contributes to the pool of active cytokines and soluble receptors. MMP-1 has been demonstrated to activate MMP-3 and stimulate tumour cell migration. A previous study by Hoffmann et al. found no differences in the plasma levels of MMP-2 between healthy controls and septic patients. Others found that MMP-2, a type IV collagenase, is present in joints and plasma of healthy controls but is activated by thrombin, suggesting that sepsis-associated decline of MMP-2 may be due to binding of selective inhibitors or transcriptional downregulation. The patterns of MMP-1, -2 and -13 are very similar suggesting that these enzymes play a major role in stress-induced tissue remodeling. Although MMP-9 and -13 may correlate in other studies, we did not find significant differences in the MMP-9 protein levels between SIRS and septic patients. Studies using MMP-9 gene deficient mice (MMP-9−/−) and normal wild-type mice both infected (i.p) with Escherichia coli showed that MMP-9 deficient mice displayed a reduced resistance against E. coli, as indicated by an enhanced bacterial outgrowth in the peritoneal cavity and increased dissemination of infection.

Next to the decreased levels of MMP in septic patients, we also found decreased levels of sE-selectin. E-selectin is an early mediator of leukocyte-endothelial adhesion, and is expressed on activated endothelium. In our study, we observed a relatively low E-selectin secretion into the blood stream as the diseases progressed from SIRS to sepsis. The vascular endothelium controls leukocyte extravasation into tissue by the induction and modulation of endothelial cell adhesion molecules, such as E-selectin (CD62E). E-selectin is not expressed by non-stimulated endothelium, but is activated by cytokines and initiates neutrophil recruitment in sepsis-induced lung injury. According
A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaegh...
interventions to influence the course of disease.

References

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74.

2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10. [PUBMED] [FULLTEXT]

3. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:158-69. [PUBMED] [FULLTEXT]

4. Le Gall JR, Lemasheb S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63. [PUBMED] [FULLTEXT]

5. 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 for Intensive Care Medicine. Intensive Care Med 1996;22:707-10.

6. Schaffer JD, Janesky M. A genetic algorithm approach for discovering diagnostic patterns in molecular measurement data. Proc. CIBCB; 2005. p. 392-9.

7. Duda RO, Hart PE, Stork DG. Pattern Classification. John Wiley and Sons; 2001.

8. Tracey KJ, Cerami A. Metabolic responses to cachectin/TNF: A brief review. Ann N Y Acad Sci 1990;587:325-31.

9. Ayabe T, Satchell DP, Pesendorfer P, Tanabe H, Wilsson CL, Hagen SJ, Ouellette AJ. Activation of Paneth cell alpha-defensins in mouse small intestine. J Biol Chem 2002;277:5219-28. [PUBMED] [FULLTEXT]

10. Somerville RP, Oatlander SA, Apte SS. Matrix metalloproteinases: Old dogs with new tricks. Genome Biol 2003;4:216. [PUBMED] [FULLTEXT]

11. Benov U, Schoenemarck MP, Mitchell TI, Rutter JL, Shimokawa K, Nagase H, et al. A novel host/tumor cell interaction activates matrix metalloproteinase 1 and mediates invasion through type I collagen. J Biol Chem 1999;274:23571-8. [PUBMED] [FULLTEXT]

12. Hoffmann U, Bertsch T, Dvortsak E, Liebetrau C, Lang S, Liebe V, et al. Matrix-metalloproteinases and their inhibitors are elevated in severe sepsis; Prognostic value of TIMP-1 in severe sepsis. Scand J Infect Dis 2006;38:667-72. [PUBMED] [FULLTEXT]

13. Sharony R, Pintucci G, Saunders PC, Grossi EA, Baumann FG, Gallyay WC, et al. Matrix metalloproteinase expression in vein grafts: Role of inflammatory mediators and extracellular signal-regulated kinases-1 and -2. Am J Physiol Heart Circ Physiol 2006;290:H1651-9. [PUBMED] [FULLTEXT]

14. Henderson BC, Sen U, Reynolds C, Moshal KS, Ovechkin A, Tyagi N, et al. Reversal of systemic hypertension-associated cardiac remodeling in chronic pressure overload myocardium by citalpine. J Exp Biol Sci 2007;3:385-92. [PUBMED] [FULLTEXT]

15. Renckens R, Roelofs JJ, Florquin S, Vander Jagt LO, et al. Matrix metalloproteinase-9 deficiency impairs host defense against abdominal sepsis. J Immunol 2006;176:3735-41.

16. Cummings CJ, Sessler CN, Beall LD, Fisher BJ, Best AM, Fowler AA 3rd. Soluble E-selectin levels in sepsis and critical illness. Correlation with infection and hemodynamic dysfunction. Am J Respir Crit Care Med 1997;156:431-7.

17. Tsokos M, Fehlauer F, Puschel K. Immunohistochemical expression of E-selectin in sepsis-induced lung injury. Int J Legal Med 2000;113:324-30.

18. Briassoulis G, Papassotiriou I, Mavrikiou M, Lazaropoulou C, Margeli A. Longitudinal course and clinical significance of TGF-beta1, sL-Selectin and sICAM-1 levels during severe acute stress in children. Clin Biochem 2007;40:299-304. [PUBMED] [FULLTEXT]

19. Ng PC, Li K, Chui KM, Leung TF, Wong RP, Chu WC, et al. IP-10 is an early diagnostic marker for identification of late-onset bacterial infection in preterm infants. Pediatr Res 2007;61:93-8. [PUBMED] [FULLTEXT]

20. Shindo S, Ogata K, Kubota K, Kojima A, Kobayashi M, Tada Y, et al. Vascular prosthetic implantation is associated with prolonged inflammation following aortic aneurysm surgery. J Artif Organs 2003;6:173-8.

21. Luster AD, Unkeless JC, Ravetch JV. Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins. Nature 1985;315:672-6.

22. Panzer U, Steinmetz OM, Paust HJ, Meyer-Schewinger C, Peters A, Turner JE, et al. Chemokine receptor CXCR3 mediates T cell recruitment and tissue injury in nephrotoxic nephritis in mice. J Am Soc Nephrol 2003;14:87-93.

23. Ovstebir O, Olsdpl OD, Brusletto B, Moller AS, Aase A, Haug KB, et al. Identification of genes particularly sensitive to lipopolysaccharide (LPS) in human monocyes induced by wild-type versus LPS-deficient Neisseria meningitidis strains. Infect Immun 2002;70:2865-9. [PUBMED] [FULLTEXT]

24. Emaus M, von Herath MG, Christen U. Cure of chronic viral infection and virus-induced type 1 diabetes by neutralizing antibodies. Clin Dev Immunol 2006;13:37-47. [PUBMED] [FULLTEXT]

25. Chvatchko Y, Hoogewerf AJ, Meyer A, Alouani S, Juillard P, Buser R, et al. A novel host/tumor cell interaction activates matrix metalloproteinase 1 and mediates invasion through type I collagen. J Biol Chem 1999;274:25371-8. [PUBMED] [FULLTEXT]

26. Ness TL, Ewing JL, Hogaboam CM, Kunkel SL. CCR4 is a key modulator of innate immune responses. J Exp Med 2000;191:1755-64. [PUBMED] [FULLTEXT]

27. Niess TL, Ewing JL, Hogaboam CM, Kunkel SL. CCR4 is a key modulator of innate immune responses. J Exp Med 2000;191:1755-64. [PUBMED] [FULLTEXT]

28. Ellefsen BD, Kristensen AT, Verrill KL, et al. Fruitful consequences of E-selectin dysfunction in a model of endotoxemia. J Immunol 2006;177:3258-65.

29. Igleias J, Mark PE, Levine JS. Elevated serum levels of the type I and type II receptors for tumor necrosis factor-alpha as predictive factors for ARF in patients with septic shock. Am J Kidney Dis 2003;41:62-75.

30. Nakae H, Naito K, Endo S. Soluble Fas and soluble Fas ligand levels in patients with acute hepatic failure. J Crit Care 2001;16:59-63. [PUBMED] [FULLTEXT]

31. Torre D, Tambini R, Manfredi M, Mangani V, Livi P, Malfassini V, et al. Circulating levels of FAS/APO-1 in patients with the systemic inflammatory response syndrome. Diagn Microbiol Infect Dis 2003;45:233-6. [PUBMED] [FULLTEXT]

32. Doughty L, Clark RS, Kaplan SS, Sasser H, Carcillo J, sFas and sFas ligand and pediatric sepsis-induced multiple organ failure syndrome. Pediatr Res 2002;52:922-7. [PUBMED] [FULLTEXT]

33. Adrie C, Bachelet M, Vayssier-Taussat M, Russo-Marie F, Bouchaert I, Adib-Conquy M, et al. Mitochondrial membrane potential and apoptosis peripheral blood monocytes in severe human sepsis. Am J Respi Crit Care Med 2001;164:389-95. [PUBMED] [FULLTEXT]

34. Melani C, Sangiulli S, Barazzetta FM, Werb Z, Colombo MP. Amino-biphosphonate-mediated MMP-9 inhibition breaks the tumor-bone marrow axis responsible for myeloid-derived suppressor cell expansion and macrophage infiltration in tumor stroma. Cancer Res 2007;67:11438-46. [PUBMED] [FULLTEXT]

Correspondence Address:
Chamindie Punyadeera
Department of Molecular Diagnostics, Philips Research, High Tech Campus 12a, 5656 AE Eindhoven
A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaeg ...
A biomarker panel to discriminate between systemic inflammatory response syndrome and sepsis and sepsis severity Punyadeera C, Schneider E M, Schaffer D, Hsu HY, Joos TO, Kriebel F, Weiss M, Verhaeg ...

11 IP-10 release assays in the diagnosis of tuberculosis infection: Current status and future directions Ruhwald, M. and Aabye, M.G. and Ravn, P. Expert Review of Molecular Diagnostics. 2012; 12(2): 175-187 [Pubmed]

12 Regulation of lymphocyte trafficking by CXC chemokine receptor 3 during septic shock Herzig, D.S. and Driver, B.R. and Fang, G. and Toliver-Kinsky, T.E. and Shute, E.N. and Sherwood, E.R. American Journal of Respiratory and Critical Care Medicine. 2012; 185(3): 291-300 [Pubmed]

13 Portal vein cytokines in the early phase of acute experimental oedematous and necrotizing porcine pancreatitis Sanna Meriläinen,Jyrki Mäkelä,Hanna Alaoja Jensen,Sebastian Dahlbacka,Siri Lehtonen,Toni Karhu,Karl-Heinz Herzig,Meeri Kröger,Vesa Koluvangas,Juha Koskenkari,Pasi Ohtonen,Tuomo Karttunen,Petri Lehenkari,Tatu Juvonen Scandinavian Journal of Gastroenterology. 2012; 47(11): 1375 [Pubmed]

14 Therapeutic efficacy of CXCR3 blockade in an experimental model of severe sepsis Daniela S Herzig,Yin Guo,Geping Fang,Tracy E Toliver-Kinsky,Edward R Sherwood Critical Care. 2012; 16(5): R168 [Pubmed]

15 IP-10 release assays in the diagnosis of tuberculosis infection: current status and future directions Morten Ruhwald,Martine G Aabye,Pernille Ravn Expert Review of Molecular Diagnostics. 2012; 12(2): 175 [Pubmed]

16 Regulation of Lymphocyte Trafficking by CXC Chemokine Receptor 3 during Septic Shock Daniela S. Herzig,Brandon R. Driver,Geping Fang,Tracy E. Toliver-Kinsky,Eric N. Shute,Edward R. Sherwood American Journal of Respiratory and Critical Care Medicine. 2012; 185(3): 291 [Pubmed]

17 Serial and panel analyses of biomarkers do not improve the prediction of bacteremia compared to one procalcitonin measurement M. Tromp,B. Lansdorp,C.P. Bleeker-Rovers,J.M. Klein Gunnewiek,B.J. Kullberg,P. Pickkers Journal of Infection. 2012; 65(4): 292 [Pubmed]

18 Propolis derivatives inhibit the systemic inflammatory response and protect hepatic and neuronal cells in acute septic shock Aida Abdelhamid Korish,Maha Mohamed Arafa The Brazilian Journal of Infectious Diseases. 2011; 15(4): 332 [Pubmed]

19 Multimarker Panels in Sepsis Brian Caserly,Richard Read,Mitchell M. Levy Critical Care Clinics. 2011; 27(2): 391 [Pubmed]

20 Role of acute ethanol exposure and TLR4 in early events of sepsis in a mouse model Minny Bhatty,Basil L. Jan,Wei Tan,Stephen B. Pruett,Bindu Nanduri Alcohol. 2011; 45(8): 795 [Pubmed]

21 Biomarkers for the differentiation of sepsis and SIRS: the need for the standardisation of diagnostic studies Hall, T.C. and Bilku, D. and Al-Leswas, C. and Horst, A. R. and Dennison, A. R. Irish Journal of Medical Science. 2011; 180(4): 793 [Pubmed]

22 Biomarkers for the differentiation of sepsis and SIRS: The need for the standardisation of diagnostic studies Hall, T.C. and Bilku, D.K. and Al-Leswas, D. and Horst, C. and Dennison, A.R. Irish Journal of Medical Science. 2011; 180(4): 793-798 [Pubmed]

23 Role of acute ethanol exposure and TLR4 in early events of sepsis in a mouse model Bhatty, M. and Jan, B.L. and Tan, W. and Pruett, S.B. and Nanduri, B. Alcohol. 2011; 45(8): 795-803 [Pubmed]

24 Gene expression profiles of immune mediators and histopathological findings in animal models of leptospirosis: Comparison between susceptible hamsters and resistant mice Matsui, M. and Rouleau, V. and Bruy`re-Ostelle, L. and Guarant, C. Infection and Immunity. 2011; 79(11): 4480-4492 [Pubmed]

25 The dynamic changes of systemic inflammatory response syndrome after cardiopulmonary resuscitation in rabbits Xiao, M. and Yang, J.-N. and Li, X.-Y. and Wang, X.-J. and Zhang, X.-G. and Lv, J. Chinese Journal of Emergency Medicine. 2011; 20(8): 830-834 [Pubmed]

26 Propolis derivatives inhibit the systemic inflammatory response and protect hepatic and neuronal cells in acute septic shock Korish, A.A. and Arafa, M.M. Brazilian Journal of Infectious Diseases. 2011; 15(4): 332-338 [Pubmed]

27 Diagnostic biomarker discovery for peanut allergy Turcanu, V. International Drug Discovery. 2011; 8(12)
| Number | Title                                                                 | Authors                                                                 | Journal                                                                 | Year | Pages |
|--------|-----------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------|------|-------|
| 28     | Multimarker Panels in Sepsis                                          | Casserly, B. and Read, R. and Levy, M.M.                              | Critical Care Clinics. 2011; 27(2): 391-405                             | 2011 | 391-405 |
| 29     | Commenting on biomarkers for differentiating between SIRS and sepsis   | Wiwanitkit, V.                                                         | Journal of Emergencies, Trauma and Shock. 2010; 3(3): 308               | 2010 | 308   |
| 30     | Authors' reply                                                        | Punyadeera, C. and Schneider, E.M. and Schaffer, D. and Hsu, H.-Y. and Joos, T.O. and Kriebel, F. and Weiss, M. and Verhaegh, W.F.J. | Journal of Emergencies, Trauma and Shock. 2010; 3(3): 308               | 2010 | 308   |