Biomarkers of Sepsis

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This was asked about in Question 9 from the second paper of 2009. Question 23 from the first paper of 2010 and the near-identicalQuestion 6 from the second paper of 2016 ask specifically about procalcitonin, because it is the hot new thing.

One can find a plethora of articles on this topic, all unimaginatively titled "Biomarkers of sepsis":

- Kibe, Adams and Barlow (2011)
- Faix (2013)
- Singer (2013)
- Henriquez-Camacho and Losa (2014)
- Cho and Choi (2014)

In brief summary:

- **ESR:** cheap, easy, but unreliable, affected by age, temperature, lab technique, and is completely nonspecific for sepsis
- **CRP:** cheap, easy, but also elevated in non-infective situations eg. MI, burns, surgery, trauma, autoimmune disease - and not as specific as procalcitonin

- **Procalcitonin:** quick, more specific for bacterial sepsis than CRP, but expensive. For the discrimination of infectious from non-infectious cause of fever, the clinical judgement of an ED physician is at least equally accurate, if not better.
  - Non-infective causes of PCt elevation: burns, massive tissue necrosis, tumour lysis, cardiac or major abdominal surgery, multi-organ system failure, ESRD, paraneoplastic production
- **Important procalcitonin trials to mention:**
  - ProSEP(2008) - reduced antibiotic exposure
  - ProSICU (2009) - reduced antibiotic exposure
  - ProVAP (2009) - reduced antibiotic exposure (after VAP onset)
  - ProRATA (2010) - reduced antibiotic exposure
  - PASS (2013) - no improvement of survival, longer stay, worse organ function!
  - SAPS (2016) - reduced antibiotic exposure, and improved 28-day survival (20% vs 25%)
- **Other weird ones to remember:**
  - Pro-adrenomedullin, LPS-binding protein, sTREM-1, presepsin, HMGB-1, CD64

To make more detail available, the markers, their properties, advantages and disadvantages have been compiled into the table below. Where possible, references to the relevant publication

are included. Elsewhere the main reference is Cho and Choi's review paper. If the time-poor exam candidate were to limit themselves to only one article, they could do much worse. Again, Oh's Manual is useless for this purpose; two paragraphs are devoted to biomarkers of sepsis on page 720 of the 7th edition (in Chapter 69 by De Gaudio).

Without further ado:

A Comparison among Laboratory Markers of Sepsis

Marker	Physiology	Advantages	Disadvantages
ESR	Erythrocyte sedimentation rate; the rate at which EDTA-treated diluted RBCs clump together in a vertical test tube. Elevated in inflammatory conditions, mainly because of the increased amount of fibrinogen, which is an acute phase reactant	Easy to perform. Requires no special equipment, and minimal technical skill Uses widely available cheap reagents. Available in resource-poor environments.	Takes about one hour to perform Completely non-specific Old-school: as sophistication of laboratories has increased, the demand for ESR testing has diminished Varies with age, temperature, test tube position... Unreliable Non-infectious causes of elevation: Malignancy (eg. multiple myeloma) Inflammatory disease, eg. RA/PMR Chronic renal failure Vasculitis, eg. temporal arteritis
CRP	C-reactive protein is the protein responsible for precipitating C-polysaccharide during the acute phase of *Streptococcus pneumonia* infection. Molecular mass ~ 115 kDa Produced by the liver Its role is as an	Cheap Easy to perform Widely available As a marker for bacterial infections: Sensitivity 68-92% Specificity 40-67% Correlates with severity of	A nonspecific marker of inflammation Non-infectious causes of elevation: Surgery, trauma Burns Myocardial infarctions Rheumatologic al disease

	opsonin; it binds to soluble or particulate ligands and activates complement. Macrophages also have CRP receptors. CRP increases 4-6hrs after the start of an infection and then doubles every 8 hours, reaching a peak at 36-50 hours Half-life of 19 hours	infection A rapid decrease in CRP levels can be interpreted as a good response to antibiotic therapy	Unreliable in patients with a dysfunctional liver Not as good as procalcitonin in discriminating infectious from non-infectious causes of fever - Pct vs. CRP meta-analysis (2004)
Procalcitonin	The prohormone of calcitonin, normally synthesised by the C-cells of the thyroid gland, but produced ectopically by neuroendocrine cells in the lung and intestine in the context of sepsis. 116-peptide molecule, 13 kDa Cleared by the parathyroid gland; its renal clearance is minimal. Synthesis is triggered by bacterial endotoxin and inflammatory cytokines. Levels peak after 6 hours. It has a half-life of 24-36 hours	Useful in early identifying occult infection; levels peak rapidly after the first appearance of endotoxin, i.e. before blood cultures have time to incubate. Useful in discriminating between bacterial and non-infectious causes of inflammation, as its synthesis is triggered by bacterial endotoxin. Quick to perform More specific for bacterial sepsis than CRP. The strong industry stimulus behind the use of procalcitonin has resulted in a massive number of trials: Pct vs. CRP meta-analysis (2004) ProSEP study (2008) PASS study (2013) ProSICU study (2009) ProVAP study (2009) ProRATA study (2010) SAPS study (2016)	Expensive Optimal use requires serial measurements, which is even more expensive. No value in assessment of fungal or viral infections No value in assessment of localised infections without a systemic response There is disagreement as to what the negative cutoff value should be. For the discrimination of infectious from non-infectious cause of fever, the clinical judgement of an ED physician is at least equally accurate, if not better. Non-infective causes of elevation: Burns Massive tissue necrosis Tumour lysis Cardiac or major abdominal surgery Multi-organ

			Recent meta-analysis (2015)	system failure Treatment with T-cell antibodies End-stage renal failure (procalcitonin is chronically elevated) Paraneoplastic production, eg. by medullary thyroid carcinoma or by small-cell lung cancer
Pro-adrenomedullin	Proadrenomedullin is the stable and physiologically inert mid-regional peptide fragment cleaved from the same precursor molecule as adrenomedullin. Adrenomedullin (ADM) is produced during physiological stress; roles include vasodilation, anti-inflammatory and antimicrobial effects. In fact it is a very potent vasodilator. It is produced by a variety of tissues: brain, lungs, heart, kidneys, endothelial cells and adipocytes. ADM is rapidly cleared from the circulation (half-life of 22 minutes) but proADM has a longer half-life. Proadrenomedullin mid-range fragment is present in the bloodstream in stoichiometrically equivalent amounts to ADM.	ProADM is higher in patients with sepsis than with SIRS In febrile neutropenia patients, proADM can distinguish sepsis from non-infectious SIRS Unlike procalcitonin, proADM rises in localised infectious processes (eg. abscesses) Also it seems to be superior to procalcitonin as a predictor of bloodstream infection, and of non-response to therapy ProADM predicts mortality in patients with community-acquired pneumonia and C OPD; at least in some of the studies	Expensive Not widely available Levels do not seem to correlate very strongly with severity Non infectious causes of elevation: Congestive heart failure Acute heart failure
LPS-binding protein	A polypeptide that binds LPS Catalyses the transfer of LPS to the CD14 marker (a part of the monocyte cellular receptor for LPS)	Levels rise severalfold in sepsis, making LBP a useful diagnostic marker of sepsis		Expensive Not widely available LPS and LBP levels are affected by administration

	Mainly synthesized in the liver. Modulates the immune response Has a dual action, enhancing and inhibiting LPS signaling at low and higher levels, respectively.		of antibiotics and generally do not correlate to the clinical course of sepsis. Affected by hepatic health, and in unexpected ways; for instance in cirrhotic patients higher LBP levels are actually associated with increased survival.
sTREM-1	Soluble triggering receptor expressed on myeloid cell 1 A soluble form of TREM-1, a glycopeptide receptor expressed on the surface of myeloid cells. Expression of sTREM-1 increases in bacterial and fungal sepsis	Probably as accurate as procalcitonin (if not better at a high cut-off) in the diagnosis of bacterial sepsis For bacterial infections: Sensitivity 82% Specificity 86% Admission sTREM-1 levels are independently associated with mortality Rapid decrease of sTREM-1 is associated with a better outcome	Expensive Not widely available A more recent meta-analysis has down-estimated its sensitivity and specificity Also elevated in acute MI Assay method significantly affects accuracy
Presepsin (sCD14-st)	Presepsin is a 13kDa protein, the the soluble N-terminal fragment of CD14 (a part of the LPS receptor from myeloid cells) During inflammation, plasma protease activity generates these CD14 fragments. Increases at 2 hours post insult, and has a half-life of 4-5 hours	Detects both systemic and localised bacterial infections: Sensitivity 87.8% Specificity 81.4% Rises very early: useful for early (emergency department) diagnosis of sepsis Prognostically important:evolution of presepsin levels was associated with outcome in the ALBIOS study Unlike	Expensive Not widely available Promising literature, but still very little of it; wide acceptance has not been gained. Enthusiasm among researchers may have the effect of obscuring the potential disadvantages Elevated in non-septic patients: Neutropenic mucositis

		procalcitonin, presepsin is not confused by the presence of severe burns Even though it is derived from WCCs, neutropenic patients still mount a high presepsin level in the presence of sepsis	○ Hepatitis (chronic HepB) ○ Febrile but culture-negative patients ○ Psoriasis Levels did not seem to increase in UTI Affected by antimyeloid drugs: lower levels are seen after chemotherapy
HMGB-1	High-mobility group box 1 protein: a cytoplasmic and nuclear protein released by activated monocytes or necrotic tissues. Undetectable in healthy subjects Rises at 8-12 hours Plateaus after 18-32 hours	HMGB-1 measurements on day 3 discriminated survivors from non-survivors with a sensitivity of 66% and specificity of 67% Correlates well with sepsis severity and degree of organ failure	Expensive Not widely available It may be a nonspecific "danger signal" rather than a sepsis-specific marker. May also be elevated in malignancy and non-infectious inflammatory states, such as colitis, SLE, arthritis, radiation injury and ischaemia.
CD64	A membrane glycoprotein expressed on the surface of activated neutrophils Expression increases hours after activation of innate immunity Not expressed by normal neutrophils	Predicts positive blood cultures Predicts bacterial infection in febrile patients with a sensitivity of 87% A meta abalysis of (poor quality) studies suggests that it is a useful marker of bacterial infection: Sensitivity 79% Specificity 91%	Expensive Not widely available Not a soluble mediator; requires some neutrophils for testing (may be tricky in neutropenia) All published studies thus far have suffered from poor methodology.

Procalcitonin in detail

The college loves procalcitonin. It has been the subject of Question 23 from the first paper of 2010 and the near-

identicalQuestion 6 from the second paper of 2016. The cancidates were asked to critically evaluate the use of procalcitonin, quoting some studies where possible. The answer to these questions is reproduced below to simplify revision:

- **Introduction / definition:**
  - Procalcitonin is the prohormone of calcitonin, normally synthesised by the C-cells of the thyroid gland, but produced ectopically by lung and intestine in the context of sepsis. As such, it is an attractive biomarker, and has been the subject of interesting research.
- **Rationale:**
  - Procalcitonin may be useful in identifying occult infection; levels peak within 6-8 hours after the first appearance of endotoxin, and this it may identify patients with severe infection before blood cultures have time to incubate, and before more serious manifestations of sepsis have time to evolve.
  - Procalcitonin may be useful in discriminating between bacterial and non-infectious causes of inflammation, as its synthesis is triggered by bacterial endotoxin
- **Evidence: what the recent trials say**
  - The college answer usually quotes the PRORATA study which suggested that the use of procalcitonin could result in reduced antibiotic exposure.
  - There are others:
    - ProSEP study (2008)
    - PASS study (2008)
    - ProSICU study (2009)
    - ProVAP study (2009)
    - ProRATA study (2010)
    - ProGUARD study (2014)
    - SAPS study (2016)
  - Overall, according to a recent meta-analysis by Hoeboer et al (2015, quoted by the college in their answer to Question 6 from the second paper of 2016)
    - *"The optimal and most widely used procalcitonin cut-off value was 0.5 ng/mL with a corresponding sensitivity of 76% and specificity of 69%"*
    - The authors concluded that procalcitonin had a "fair" diagnostic accuracy for bacteraemia.

        - According to an old meta-analysis (2004), it was more sensitive and more specific than CRP.
- **Advantages**
    - Quick to perform the assay
    - More specific for bacterial sepsis than CRP
    - Getting cheaper
    - Predictor of outcome - high levels associated with higher mortality and unexpected ICU readmission (Zhou et al, 2016)
    - Persistently high levels are associated with worse organ dysfunction (Hatherill et al, 2000 - as well as many other studies which confirmed this association)
    - Guides antibiotic therapy in the absence of better guesses (eg. where infectious diseases physicians are not available for an opinion)
    - Accurate in identifying bacterial sepsis -a meta-analysis by Wacker et al (2013) found an AUROC of 0.85, and Meynaar et al (2011) found a positive predictive value of 88%.
    - Better than CRP for bacterial sepsis (higher sensitivity, similar specificity - Simon et al, 2004)
- **Disadvantages**
    - Expensive
    - Optimal use requires serial measurements, which is even more expensive.
    - Confounded by non-infectious conditions, such as...
        - Extreme inflammatory stimuli:
            - Burns
            - Massive tissue necrosis
            - Tumour lysis
            - Cardiac or major abdominal surgery
            - Multi-organ system failure
        - Treatment with T-cell antibodies
        - End-stage renal failure (procalcitonin is chronically elevated)
    - No value in assessment of fungal or viral infections
    - No value in assessment of localised infections without a systemic response
    - There is disagreement as to what the negative cutoff value should be.
    - For the discrimination of infectious from non-infectious cause of fever, the clinical judgement of an ED physician is at least equally accurate, if not better.

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References

Povoa, P., et al. "C-reactive protein as an indicator of sepsis." *Intensive care medicine* 24.10 (1998): 1052-1056.

Wacker, Christina, et al. "Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis." *The Lancet infectious diseases* 13.5 (2013): 426-435.

Opal, Steven M., et al. "Relationship between plasma levels of lipopolysaccharide (LPS) and LPS-binding protein in patients with severe sepsis and septic shock." *Journal of Infectious Diseases* 180.5 (1999): 1584-1589.

Shozushima, Tatsuyori, et al. "Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome."*Journal of Infection and Chemotherapy* 17.6 (2011): 764-769.

Gámez-Díaz, Laura Y., et al. "Diagnostic Accuracy of HMGB-1, sTREM-1, and CD64 as Markers of Sepsis in Patients Recently Admitted to the Emergency Department." *Academic Emergency Medicine* 18.8 (2011): 807-815.

Kwofie, L., et al. "Evaluation of circulating soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) to predict risk profile, response to antimicrobial therapy, and development of complications in patients with chemotherapy-associated febrile neutropenia: a pilot study." *Annals of hematology* 91.4 (2012): 605-611.

Gros, Antoine, et al. "The sensitivity of neutrophil CD64 expression as a biomarker of bacterial infection is low in critically ill patients." *Intensive care medicine* 38.3 (2012): 445-452.

Gámez-Díaz, Laura Y., et al. "Diagnostic Accuracy of HMGB-1, sTREM-1, and CD64 as Markers of Sepsis in Patients Recently

Admitted to the Emergency Department." *Academic Emergency Medicine* 18.8 (2011): 807-815.

Calfee, Carolyn S., and Jérôme Pugin. "The search for diagnostic markers in sepsis: many miles yet to go." *American journal of respiratory and critical care medicine* 186.1 (2012): 2-4.

Faix, James D. "Biomarkers of sepsis*." *Critical reviews in clinical laboratory sciences* 50.1 (2013): 23-36.

Singer, Mervyn. "Biomarkers in sepsis." *Current opinion in pulmonary medicine*19.3 (2013): 305.

Kibe, Savitri, Kate Adams, and Gavin Barlow. "Diagnostic and prognostic biomarkers of sepsis in critical care." *Journal of antimicrobial chemotherapy*66.suppl 2 (2011): ii33-ii40.

Henriquez-Camacho, Cesar, and Juan Losa. "Biomarkers for Sepsis." *BioMed research international* 2014 (2014).

Cho, Sung-Yeon, and Jung-Hyun Choi. "Biomarkers of sepsis." *Infection & chemotherapy* 46.1 (2014): 1-12.

Zacharski, Leo R., and Robert A. Kyle. "Significance of extreme elevation of erythrocyte sedimentation rate." *Jama* 202.4 (1967): 264-266.

BANNICK, EDWIN G., ROBERT O. GREGG, and CHESTER M. GUERNSEY. "The erythrocyte sedimentation rate: the adequacy of a simple test and its practical application in clinical medicine." *Journal of the American Medical Association* 109.16 (1937): 1257-1262.

Hameed, M. Amjad, and Sobia Waqas. "Physiological basis and clinical utility of erythrocyte sedimentation rate." *Pak J Med Sci 2006; 22: p214* 217 (2006).

Saadeh, Constantine, and Tex Amarillo. "The erythrocyte sedimentation rate: old and new clinical applications" *South Med J.* 1998 Mar;91(3):220-5.

Tillett, William S., and Thomas Francis. "Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus." *The Journal of experimental medicine* 52.4 (1930): 561-571.

Vincent, Jean-Louis, Katia Donadello, and Xavier Schmit. "Biomarkers in the critically ill patient: C-reactive protein." *Critical care clinics* 27.2 (2011): 241-251.

Povoa, P., et al. "C-reactive protein as a marker of infection in critically ill patients." *Clinical microbiology and infection* 11.2 (2005): 101-108.

Schmit, Xavier, and Jean Louis Vincent. "The time course of blood C-reactive protein concentrations in relation to the response to initial antimicrobial therapy in patients with sepsis." *Infection* 36.3 (2008): 213-219.

Kushner, I. R. V. I. N. G., and G. E. R. A. R. D. Feldmann. "Control of the acute phase response. Demonstration of C-reactive protein synthesis and secretion by hepatocytes during acute inflammation in the rabbit." *The Journal of experimental medicine* 148.2 (1978): 466-477.

Vigushin, David M., Mark B. Pepys, and Philip N. Hawkins. "Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease." *Journal of clinical investigation* 91.4 (1993): 1351.

Maruna, P., K. Nedelnikova, and R. Gurlich. "Physiology and genetics of procalcitonin." *Physiological Research* 49 (2000): S57-S62.

Delevaux, I., et al. "Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes?."*Annals of the rheumatic diseases* 62.4 (2003): 337-340.

Maniaci, Vincenzo, et al. "Procalcitonin in young febrile infants for the detection of serious bacterial infections." *Pediatrics* 122.4 (2008): 701-710.

Becker, Kenneth L., Richard Snider, and Eric S. Nylen. "Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations."*Critical care medicine* 36.3 (2008): 941-952.

Limper, Maarten, et al. "The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever." *Journal of Infection* 60.6 (2010): 409-416.

Höflich, R. Sabat C., and W. D. Döcke. "Massive elevation of procalcitonin plasma levels in the absence of infection in kidney transplant patients treated with pan-T-cell antibodies." *Intensive Care Med* 27 (2001): 987-991.

Wacker, Christina, et al. "Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis." *The Lancet infectious diseases* 13.5 (2013): 426-435.

Hausfater, Pierre, et al. "Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department." *Critical Care* 11.3 (2007): R60.

Bouadma, Lila, et al. "Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial." *The Lancet* 375.9713 (2010): 463-474.

Maruna, P., K. Nedelnikova, and R. Gurlich. "Physiology and genetics of procalcitonin." *Physiological Research* 49 (2000): S57-S62.

Assink-de Jong, Evelien, et al. "Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicenter investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard-of-care approach can safely shorten antibiotic duration in intensive care unit patients-calculated sample size: 1816 patients." *BMC infectious diseases* 13.1 (2013): 178.

Jensen, Jens-Ulrik, et al. "The Procalcitonin And Survival Study (PASS)–a randomised multi-center investigator-initiated trial to investigate whether daily measurements biomarker Procalcitonin and pro-active diagnostic and therapeutic responses to abnormal Procalcitonin levels, can improve survival in intensive care unit patients. Calculated sample size (target population): 1000 patients." *BMC infectious diseases* 8.1 (2008): 91.

Nobre, Vandack, et al. "Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial." *American journal of respiratory and critical care medicine* 177.5 (2008): 498.

Jensen, Jens U., et al. "Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve

survival in the intensive care unit: A randomized trial*." *Critical care medicine* 39.9 (2011): 2048-2058.

Hochreiter, Marcel, et al. "Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial." *Crit Care*13.3 (2009): R83.

Stolz, Daiana, et al. "Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study." *European Respiratory Journal*34.6 (2009): 1364-1375.

Hoeboer, Sandra H., et al. "The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis." *Clinical Microbiology and Infection* (2015).

Simon, Liliana, et al. "Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis." *Clinical Infectious Diseases* 39.2 (2004): 206-217.

Linscheid, Philippe, et al. "Autocrine/paracrine role of inflammation-mediated calcitonin gene-related peptide and adrenomedullin expression in human adipose tissue." *Endocrinology* 146.6 (2005): 2699-2708.

Christ-Crain, Mirjam, et al. "Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study." *Crit Care* 9.6 (2005): R816-R824.

Al Shuaibi, Munirah, et al. "Pro-adrenomedullin as a novel biomarker for predicting infections and response to antimicrobials in febrile patients with hematologic malignancies." *Clinical infectious diseases* 56.7 (2013): 943-950.

Debiane, Labib, et al. "The Utility of Proadrenomedullin and Procalcitonin in Comparison to C-Reactive Protein as Predictors of Sepsis and Bloodstream Infections in Critically Ill Patients With Cancer*." *Critical care medicine* 42.12 (2014): 2500-2507.

Cavallazzi, Rodrigo, et al. "Midregional proadrenomedullin for prognosis in community-acquired pneumonia: A systematic review." *Respiratory medicine*108.11 (2014): 1569-1580.

Zuur-Telgen, Maaike C., et al. "Stable-state midrange-proadrenomedullin level is a strong predictor of mortality in patients with COPD." *CHEST Journal* 145.3 (2014): 534-541.

Funke-Kaiser, Anne, et al. "Predictive value of midregional pro-adrenomedullin compared to natriuretic peptides for incident cardiovascular disease and heart failure in the population-based FINRISK 1997 cohort." *Annals of medicine* 46.3 (2014): 155-162.

Akpinar, Serdar, et al. "Performance evaluation of MR-proadrenomedullin and other scoring systems in severe sepsis with pneumonia." *Journal of thoracic disease* 6.7 (2014): 921.

Struck, Joachim, et al. "Identification of an adrenomedullin precursor fragment in plasma of sepsis patients." *Peptides* 25.8 (2004): 1369-1372.

Potocki, Mihael, Ronny Ziller, and Christian Mueller. "Mid-regional pro-adrenomedullin in acute heart failure: a better biomarker or just another biomarker?." *Current heart failure reports* 9.3 (2012): 244-251.

Jerala, Roman. "Structural biology of the LPS recognition." *International Journal of Medical Microbiology* 297.5 (2007): 353-363.

Choi, Jung Hyun, and Wan Shik Shin. *Korean Journal of Infectious Diseases* 32.2 (2000): 148-157."Pathogenesis of sepsis and concepts of immunotherapy."

Zweigner, Janine, et al. "High concentrations of lipopolysaccharide-binding protein in serum of patients with severe sepsis or septic shock inhibit the lipopolysaccharide response in human monocytes." *Blood* 98.13 (2001): 3800-3808.

Chen, Yi-Yuan, et al. "Lipopolysaccharide binding protein in cirrhotic patients with severe sepsis." *Journal of the Chinese Medical Association* 77.2 (2014): 68-74.

Gibot, Sébastien. "Clinical review: role of triggering receptor expressed on myeloid cells-1 during sepsis." *CRITICAL CARE-LONDON*- 9.5 (2005): 485.

Gibot, Sébastien, et al. "Plasma level of a triggering receptor expressed on myeloid cells-1: its diagnostic accuracy in patients with suspected sepsis."*Annals of Internal Medicine* 141.1 (2004): 9-15.

Jiyong, Jing, et al. "Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in bacterial infection: a meta-analysis." *Intensive care medicine* 35.4 (2009): 587-595.

Wu, Youping, et al. "Accuracy of plasma sTREM-1 for sepsis diagnosis in systemic inflammatory patients: a systematic review and meta-analysis." *Crit Care* 16.6 (2012): R229.

Jeong, Su Jin, et al. "Measurement of plasma sTREM-1 in patients with severe sepsis receiving early goal-directed therapy and evaluation of its usefulness."*Shock* 37.6 (2012): 574-578.

Oufella, Hafid Ait, et al. "Circulating Levels of sTREM-1 and Mortality in Patients With an Acute Myocardial Infarction." *Circulation* 130.Suppl 2 (2014): A16204-A16204.

Endo, Shigeatsu, et al. "Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study." *Journal of Infection and Chemotherapy* 18.6 (2012): 891-897.

Olad, Elham, et al. "Presepsin (Scd14) as a Marker of Serious Bacterial Infections in Chemotherapy Induced Severe Neutropenia." *Iranian Journal of Pediatrics* 24.6 (2014): 715-722.

Ulla, Marco, et al. "Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study." *Crit Care* 17.4 (2013): R168.

Masson, Serge, et al. "Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial." *Crit Care* 18.1 (2014): R6.

Ramana, K. V., et al. "Presepsin: A Novel and Potential Diagnostic Biomarker for Sepsis." *American Journal of Medical and Biological Research* 2.4 (2014): 97-100.

Madenci, Özlem Çakır, et al. "Evaluation of soluble CD14 subtype (presepsin) in burn sepsis." *Burns* 40.4 (2014): 664-669.

Gibot, Sébastien, et al. "High-mobility group box 1 protein plasma concentrations during septic shock." *Intensive care medicine* 33.8 (2007): 1347-1353.

Sundén-Cullberg, Jonas, et al. "Persistent elevation of high mobility group box-1 protein (HMGB1) in patients with severe sepsis and septic shock*." *Critical care medicine* 33.3 (2005): 564-573.

Klune, John R., et al. "HMGB1: endogenous danger signaling." *Molecular Medicine* 14.7-8 (2008): 476.

Icardi, M., et al. "CD64 index provides simple and predictive testing for detection and monitoring of sepsis and bacterial infection in hospital patients."*Journal of clinical microbiology* 47.12 (2009): 3914-3919.

Cid, Joan, et al. "Neutrophil CD64: diagnostic accuracy and prognostic value in patients presenting to the emergency department." *European journal of clinical microbiology & infectious diseases* 30.7 (2011): 845-852.

Cid, Joan, et al. "Neutrophil CD64 expression as marker of bacterial infection: a systematic review and meta-analysis." *Journal of Infection* 60.5 (2010): 313-319.

Jensen, Jens U., et al. "Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial." *Critical care medicine* 39.9 (2011): 2048-2058.

de Jong, Evelien, et al. "Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial." *The Lancet Infectious Diseases*(2016).

Hoeboer, Sandra H., et al. "The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis." *Clinical Microbiology and Infection* 21.5 (2015): 474-481.

Zhou, George, and Kwok M. Ho. "Procalcitonin concentrations as a predictor of unexpected readmission and mortality after intensive care unit discharge: A retrospective cohort study." *Journal of critical care* 33 (2016): 240-244.

Shehabi, Yahya, et al. "Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial." *American journal of respiratory and critical care medicine* 190.10 (2014): 1102-1110.

Matsumura, Yosuke, et al. "Serum procalcitonin level and SOFA score at discharge from the intensive care unit predict post-intensive care unit mortality: a prospective study." *PloS one* 9.12 (2014): e114007.

Azevedo, José Raimundo Araujo de, et al. "Procalcitonin as a prognostic biomarker of severe sepsis and septic shock." *Revista do Colégio Brasileiro de Cirurgiões* 39.6 (2012): 456-461.

Hatherill, Mark, et al. "Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock." *Critical care medicine* 28.7 (2000): 2591-2594.

Wacker, Christina, et al. "Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis." *The Lancet infectious diseases* 13.5 (2013): 426-435.

Meynaar, Iwan A., et al. "In critically ill patients, serum procalcitonin is more useful in differentiating between sepsis and SIRS than CRP, Il-6, or LBP." *Critical care research and practice* 2011 (2011).

Simon, Liliana, et al. "Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis." *Clinical Infectious Diseases* 39.2 (2004): 206-217.