REVIEW

IL-1β/IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections

Jeroen Slaats*, Jaap ten Oever, Frank L. van de Veerdonk, Mihai G. Netea

Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands

* H.Slaats@radboudumc.nl

Abstract

The host inflammatory response against infections is characterized by the release of pro-inflammatory cytokines and acute-phase proteins, driving both innate and adaptive arms of the immune response. Distinct patterns of circulating cytokines and acute-phase responses have proven indispensable for guiding the diagnosis and management of infectious diseases. This review discusses the profiles of acute-phase proteins and circulating cytokines encountered in viral and bacterial infections. We also propose a model in which the inflammatory response to viral (IL-18/ferritin) and bacterial (IL-6/CRP) infections presents with specific plasma patterns of immune biomarkers.

The Inflammatory Response

Inflammation is a protective response by the body that aims to remove invading pathogens, neutralize noxious stimuli, and initiate tissue repair. Inflammation is triggered when innate immune cells sense evolutionary conserved structures on pathogens (pathogen-associated molecular patterns [PAMPs]) or endogenous stress signals (damage-associated molecular patterns [DAMPs]) through germline-encoded pattern recognition receptors (PRRs). PRRs are mainly expressed by macrophages and dendritic cells, although they have also shown to be expressed by other immune and non-immune cells including neutrophils, lymphocytes, fibroblasts, and epithelial cells [1]. During an infection, cell stress provoked by invading pathogens also leads to the release of DAMPs that synergize with PAMPs to activate PRRs. The role of DAMPs in PRR activation is particularly pronounced during viral infections as viral spread depends on the fate of infected cells.

PRR activation triggers a complex array of inflammatory processes through the release of proinflammatory cytokines, with the induction of acute phase proteins (APPs) being a prominent feature of the inflammatory cascade (Fig 1). APPs comprise a homeostasis-restoring class of proteins whose plasma concentration increases in response to inflammatory insults. Plasma inflammatory cytokines and APPs have been established as a valuable tool in the diagnosis, management, and prognosis of inflammatory diseases, given their exceptional sensitivity for systemic inflammation [2]. Because inflammatory cytokines and APPs are highly heterogeneous with a wide variety of biological functions, we asked ourselves whether we could discriminate between different types of inflammatory reactions based on distinct cytokine/APP profiles. This review discusses APPs and major cytokines involved in viral- and bacterial-
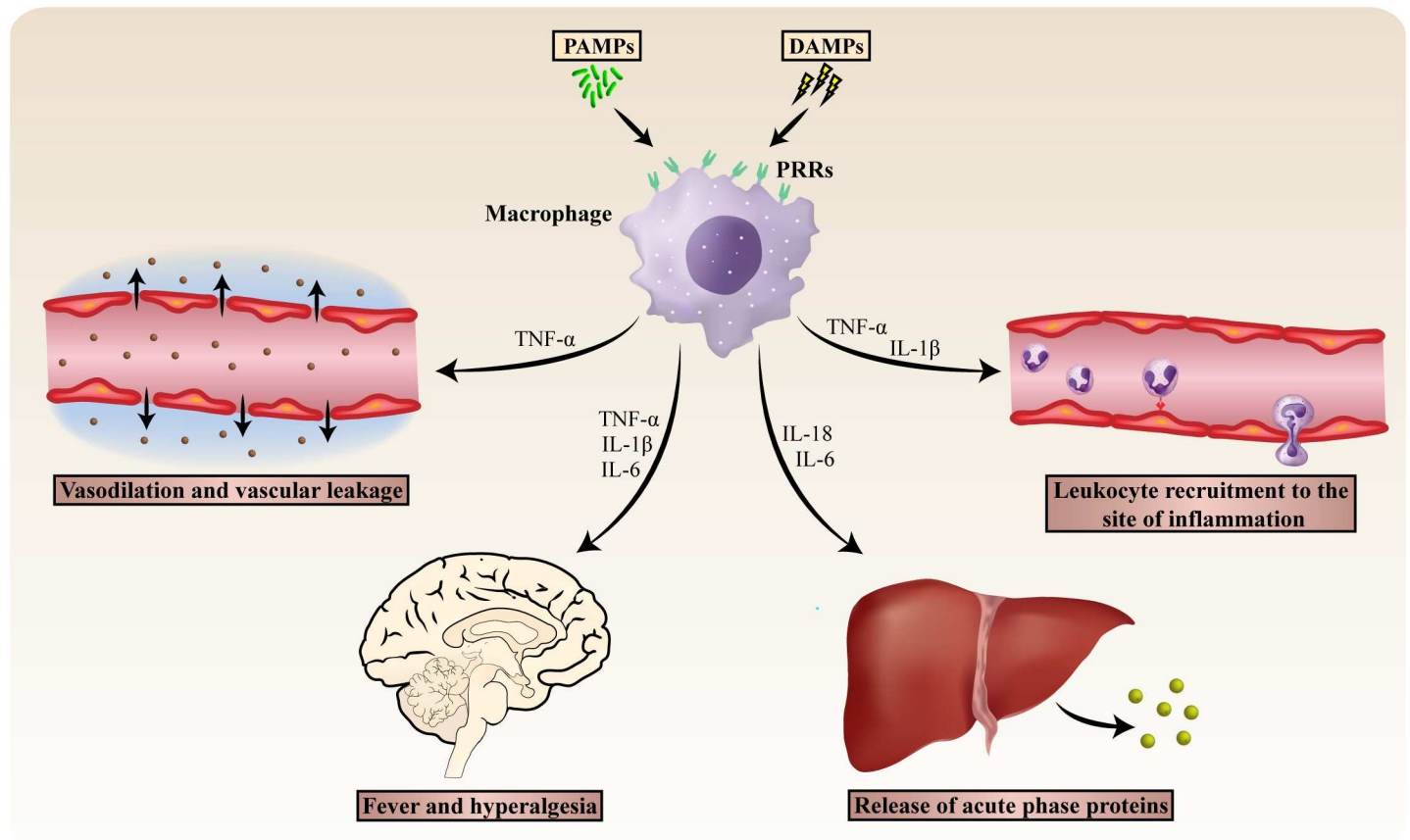
Fig 1. The acute inflammatory response mediated by the release of pro-inflammatory cytokines. Following PAMP or DAMP recognition, PRRs trigger proinflammatory and antimicrobial responses by inducing the release of a broad range of cytokines. The archetypical pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 are rapidly released upon PRR activation, and they all act as endogenous pyrogens by increasing the hypothalamic thermoregulatory set-point [82]. In addition, TNF-α and IL-1β orchestrate the release of chemokines and expression of leukocyte adhesion molecules on vascular endothelium, promoting the rapid and efficient recruitment of leukocytes towards inflammatory foci [83–85]. TNF-α is also responsible for multiple hallmark signs of inflammation by inducing local vasodilation (rubor, calor) and vascular leakage (causing swelling) [86, 87]. Furthermore, IL-1β evokes inflammatory hyperalgesia and is well known for its induction of IL-6 [88, 89]. IL-6, in turn, is a major inducer of acute-phase protein production by hepatocytes [90]. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; PRR, pattern recognition receptor.

doi:10.1371/journal.ppat.1005973.g001

induced inflammation and proposes a novel model in which two types of inflammatory reactions present with differential plasma levels of immune biomarkers. We also aim to propose a pathophysiological distinction between the induction of the acute phase response in bacterial versus viral infection.

Plasma Cytokine Markers of Inflammation

Plasma cytokine profiling is routinely used in patients with inflammation to define the pathophysiological phenotype, thereby playing a pivotal role in the diagnosis and therapeutic decision-making. The pro-inflammatory cytokines IL-1α, IL-1β, and IL-18 are inflammatory plasma markers belonging to the IL-1 family of cytokines, which are all synthesized as precursor proteins. The IL-1α precursor (pro-IL-1α) is biologically active and can be found constitutively inside cells under homeostatic conditions [3]. Pro-IL-1α is passively released from dead, dying, or injured non-apoptotic cells and acts as a major DAMP capable of triggering powerful inflammatory responses [4]. IL-1β and IL-18 are mainly produced by monocytes/macrophages in response to PAMP/DAMP recognition by PRRs [5]. Unlike pro-IL-1α, the precursors of

IL-1β and IL-18 (pro-IL-1β and pro-IL-18) are biologically inactive and require proteolytic cleavage into biologically active mature cytokines. This proteolytic cleavage mostly depends on caspase-1 activation through the formation of multimeric protein complexes termed inflammasomes. Hence, a two-step model has been proposed: first, activation of PRRs on host cells induces transcription of pro-IL-1β and pro-IL-18; second, activation of the inflammasome by PAMPs or DAMPs results in the posttranslational cleavage of the pro-cytokines into mature IL-1β and IL-18 [5].

Although the release of IL-1β and IL-18 involves similar processes, their functions differ considerably. In synergism with IL-12, IL-18 acts as bridge to link the innate immune response to IFN-γ production by driving T-helper (Th) 1 polarization and priming NK cells, both resulting in high-level production of IFN-γ [6, 7]. IFN-γ is crucial for early host defense against infections by stimulating the phagocytosis and intracellular killing of pathogens, particularly intracellular bacteria and fungi. IFN-γ also plays an important role in establishing an antiviral state for long-term control through the induction of key antiviral enzymes, most notably protein kinase R [8]. In addition, IL-18 harbors the unique property of inducing Fas ligand expression on NK cells, facilitating their killing of infected cells by Fas-mediated apoptosis [9].

In contrast to IL-18, IL-1β negatively regulates IFN-γ-mediated responses. IL-1β is a potent inducer of COX-2 expression, leading to the production of large amounts of prostaglandin E2 (PGE2). PGE2, in turn, directly acts on T cells to suppress IFN-γ production, thereby suppressing Th1 immunity and driving Th17 polarization [10]. Another downstream action of IL-1β involves upregulation of the pleotropic cytokine IL-6, which is a key factor in priming naïve T cells for Th17 differentiation [11]. IL-6 can also inhibit the immunosuppressive functions of regulatory T cells and prevent Th17 cells from converting into regulatory T cells, illustrating a pivotal role for IL-6 in shaping the adaptive immune response in favor of Th17 immunity [12, 13]. Th17 responses, which are characterized by the production and release of IL-17 and IL-22, are critical for epithelial and mucosal host defense against extracellular bacteria and fungi [14]. IL-17 and IL-22 cooperatively enhance mucosal barrier function by stimulating the expression of antimicrobial peptides and inducing neutrophil recruitment [14, 15]. Interestingly, Th17 responses may contribute to a suboptimal host defense against viruses by upregulation of anti-apoptotic molecules, thereby blocking target cell destruction by cytotoxic T cells and enhancing the survival of virus-infected cells [16]. Thus, although Th17 responses are very efficient in orchestrating the clearance of extracellular bacteria and fungi, the killing of intracellular pathogens such as intracellular bacteria and viruses may be more effective in the setting of a strong Th1 response.

Acute-Phase Proteins

To assess the presence of inflammation in a clinical setting, laboratories routinely assess the plasma concentrations of various APPs as robust biomarkers of inflammation. APPs are produced primarily by hepatocytes in response to various inflammatory cytokines, most notably IL-1β and IL-6, although IL-18 has also been implicated in APP release [17]. C-reactive protein (CRP) is the prototype of human APPs. In healthy individuals, CRP is found in trace amounts with a median plasma concentration of 0.8 mg/L, while CRP values rise sharply up to 1,000-fold after an inflammatory stimulus [18]. CRP remains stable over prolonged time periods and has a half-life of 19–20 hours [19]. Because this half-life remains constant under conditions of health and disease, the sole determinant of circulating CRP is its synthesis rate, which directly reflects the intensity of the inflammatory process [19]. This makes CRP a powerful marker for disease activity in infectious and inflammatory diseases.

CRP plays an important role in innate immunity as early defense mechanism against infections. After binding to microbial polysaccharides or ligands exposed on damaged cells, CRP can directly mediate their phagocytosis by engaging with Fc-receptors on phagocytic cells [20, 21]. Ligand-bound CRP can also mediate phagocytosis indirectly by activation of the classical complement pathway through interaction with C1q [22]. This activation process results in C3/C4 opsonization of pathogens and apoptotic cells, enhancing complement receptor-mediated phagocytosis. However, CRP attenuates the formation of a downstream membrane attack complex on the surface of invading microbes or damaged cells through recruitment of factor H, thereby protecting the cells from lysis [23]. Thus, activation of the complement cascade by CRP limits the inflammatory response by promoting opsonization while avoiding the pro-inflammatory effects of cell lysis.

Another inflammatory plasma marker that has been extensively used in clinical practice is the APP ferritin. Ferritin is a ubiquitous intracellular iron storage protein composed of 24 light (L) and heavy (H) ferritin monomers. By storing iron in a non-toxic form, ferritin prevents iron from catalyzing radical formation through Haber-Weiss or Fenton chemistry. During infection and inflammation, iron is withdrawn from the circulation and is redirected to hepatocytes and macrophages, thereby reducing the availability of this essential nutrient to invading pathogens [24]. The resulting iron overload in hepatocytes and macrophages enhances the translation of ferritin through the iron response protein [25]. Part of the elevated ferritin load in macrophages may translocate to the lysosomal compartment, where it protects this compartment from reactive iron, followed by ferritin secretion through the secretory-lysosomal pathway [26]. Ferritin may also enter the circulation via the classical ER/Golgi-dependent secretory pathway in hepatocytes [27, 28]. Another possible mechanism for ferritin secretion involves leakage from damaged cells, explaining the firm association between serum ferritin and markers of hepatocellular damage [29]. It is, however, important to note that circulating ferritin lacks most of the iron it contained when being intracellular.

Although many aspects of the fundamental biology of serum ferritin remain surprisingly unclear, various immune regulatory roles have been attributed to extracellular ferritin. Unlike L-ferritin, H-ferritin modulates the immune response by suppressing lymphocyte blastogenesis and myelopoiesis, possibly through inhibition of transferrin-mediated iron uptake, as iron is required for cell proliferation and differentiation [30–32]. H-ferritin also downregulates the immune response through induction of the anti-inflammatory cytokine IL-10 by regulatory T cells [33]. In addition, H-ferritin physically interacts with the chemokine receptor CXCR4, thereby attenuating CXCR4-mediated leukocyte migration to inflammatory sites [34]. It remains, however, paradoxical that circulating ferritin predominantly consists of L subunits, whereas most evidence supports immune modulatory functions for H-ferritin.

Besides CRP and ferritin, various other APPs have been used in clinical practice. One such protein is serum amyloid A (SAA), whose plasma concentration can rapidly increase up to 1,000-fold in response to inflammatory stimuli [35]. SAA is mainly produced in the liver and serves as an innate recognition molecule that opsonizes gram-negative bacteria for phagocytosis [36]. SAA also induces powerful and rapid secretion of proinflammatory cytokines by monocytes and macrophages, thereby augmenting the early host response to invading pathogens [37, 38]. Another fast-responding APP that has been of particular interest is the prohormone procalcitonin. Procalcitonin is secreted by parafollicular C-cells of the thyroid gland under normal conditions but can be secreted by numerous other cell types throughout the body in response to proinflammatory stimulation, culminating in markedly elevated serum procalcitonin levels [39]. However, the exact physiological function of procalcitonin during the acute phase response remains obscure and requires further study.

Plasma Inflammatory Profiles in Viral and Bacterial Infections

One of the most frequent challenges that physicians face in clinical practice is the difficulty of discriminating between viral and bacterial infections. Timely discrimination between viral and bacterial etiologies is not only required for appropriate treatment but can also prevent unnecessary morbidity and even mortality. A rapid and powerful tool that assists in the diagnosis of infectious diseases is the monitoring of host immune responses through circulating cytokines and APPs.

An interesting pattern of inflammatory plasma markers emerges in bacterial infections. Many bacterial diseases are characterized by elevated levels of circulating IL-1β and IL-6 with a concomitant increase in plasma CRP, explaining the good correlation between plasma levels of IL-6 and CRP [40]. It has been shown that circulating concentrations of both IL-6 and CRP are markedly higher in patients with community-acquired bacterial infections as compared to patients with viral infections [41]. In addition, plasma IL-6 and CRP concentrations are significantly more elevated in bacterial enterocolitis as compared to viral enterocolitis [42]. The combination of IL-6 and CRP plasma biomarkers can even be used to predict serious bacterial infections in young febrile infants [43]. Importantly, IL-6–induced CRP levels are able to distinguish between specific viral and bacterial etiologies that remain daunting challenges in clinical practice, including the discrimination between bacterial pneumonia and influenza infections as well as the discrimination between streptococcal pharyngitis and infectious mononucleosis [44].

Unlike many bacterial infections, viral infections are commonly characterized by elevated plasma levels of the pro-inflammatory cytokine IL-18, together with increased circulating ferritin concentrations. In healthy adults, IL-18 circulates in relatively low concentrations of less than 200 pg/mL, while circulating ferritin concentrations are usually in the range of 120 μg/L [45, 46]. However, during the acute stages of an Epstein-Barr virus (EBV) infection, plasma IL-18 concentrations can easily exceed 1,000 pg/mL, with median ferritin up to 431 μg/L [47]. IL-18 and ferritin are also strongly induced during chronic hepatitis B and C virus infections [48–51]. The human immunodeficiency virus (HIV) disease is another viral infection that has been characterized by increased circulating levels of both IL-18 and ferritin. During HIV infection, plasma IL-18 levels exceed 1,000 pg/mL [52, 53]. In addition, circulating ferritin in HIV patients ranges around a median of 487 μg/L and has been associated with HIV disease progression [54, 55]. The most striking elevation of circulating ferritin is seen in patients suffering from acute dengue infections, with median plasma ferritin levels up to 1,264 μg/L [56, 57]. Moreover, circulating levels of both IL-18 and ferritin show strong correlation with dengue disease severity and, therefore, may be considered as a tool to predict disease progression [57, 58]. It is, however, important to note that elevated levels of circulating IL-18 in dengue virus infections concur with increased levels of the antagonistic IL-18 binding protein (IL-18BP), resulting in unchanged plasma concentrations of free, biologically active IL-18 [59]. This demonstrates that special attention should be paid to circulating levels of free IL-18 molecules when studying the IL-18 response in infectious diseases, particularly because the ELISA kits for IL-18 detection measure the mature form of the cytokine, both free and complexed with IL-18BP. Besides its role in infectious diseases, IL-18 has been implicated in the pathophysiology of various other diseases, but this falls outside the scope of this review and has been reviewed extensively in earlier reviews (see [60]).

Although bacterial infections are commonly characterized by the induction of IL-6 and CRP, viral infections are generally associated with marked elevation in plasma IL-18 and ferritin with concomitant low circulating CRP levels (Fig 2A) [47]. Therefore, we propose a model in which bacterial- and viral-induced inflammatory responses present with differential plasma
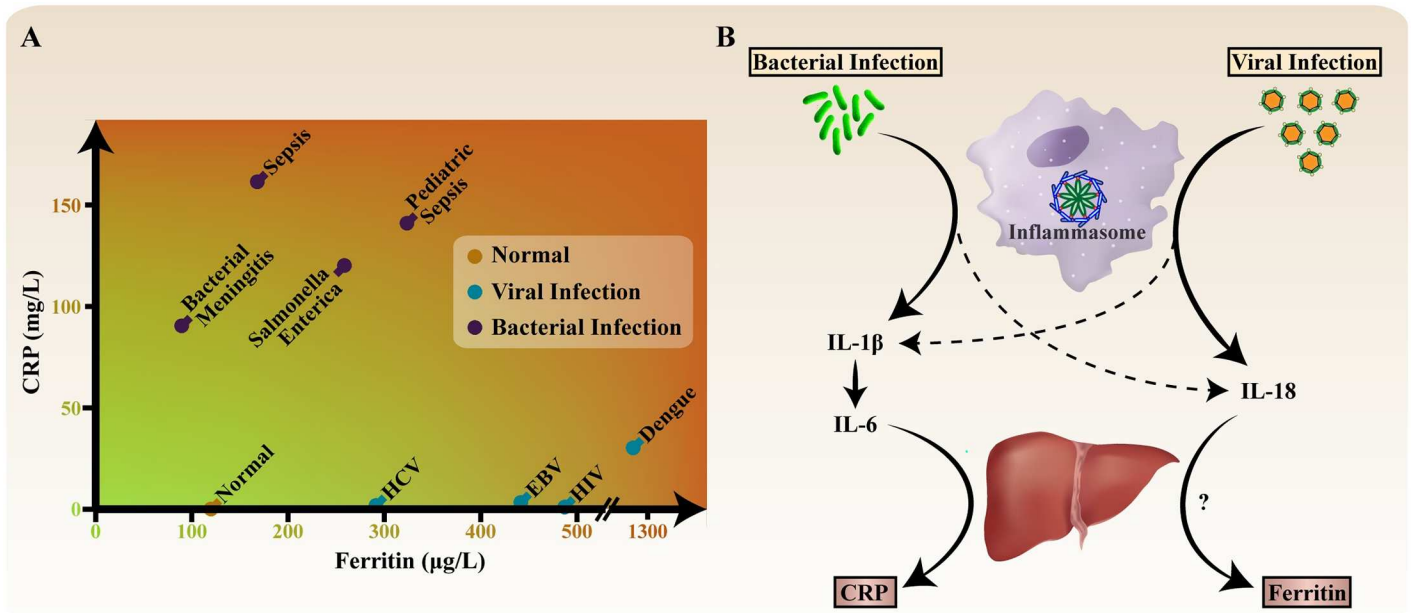
Fig 2. Bacterial- and viral-induced inflammation are characterized by differential plasma levels of CRP and ferritin. (**A**) Mean or median concentrations of circulating CRP and ferritin in various viral and bacterial infections illustrate that viral infections are generally characterized by high plasma ferritin with concomitant low circulating CRP [18, 45, 47, 54, 57, 91–94], while bacterial infections are commonly characterized by high plasma CRP levels [95–100]. (**B**) Proposed model in which the induction of IL-1β/IL-6 in response to bacterial infections contributes to elevated plasma levels of CRP, while viral infections are characterized by an IL-18 response, culminating in hyperferritinemia. Importantly, IL-1/IL-6/CRP and IL-18/ferritin do not fully reflect the bacterial-viral infection dichotomy, as various bacterial infections are known to elevate plasma IL-18 levels while some viral infections are known to raise plasma IL-1β levels [72, 73]. The direct correlation between circulating concentrations of IL-18 and ferritin has not yet been investigated and should be assessed in future studies. HCV: hepatitis C virus infection; EBV: Epstein-Barr virus infection; HIV: human immunodeficiency virus infection.

levels of CRP and ferritin (Fig 2B). Upon viral infection, IL-18 release induces a marked elevation of circulation ferritin, explaining the frequently observed hyperferritinemia in viral infections. IL-18 also stimulates Th1 immune responses, which play a crucial role in the host defense against intracellular microbes through the induction of IFN-γ. In contrast, bacterial infections are commonly associated with an extensive release of IL-1β, thereby stimulating the hepatocytic CRP secretion through the induction of IL-6. CRP, in turn, acts as innate weapon in early host defense by promoting the phagocytosis of bacteria. IL-1β also stimulates a Th17 immune response, which is crucial for epithelial and mucosal defense against extracellular bacteria. Thus, the IL-18 response in viral infections is responsible for hyperferritinemia, while bacterial infections are characterized by an IL-1β/IL-6 response, culminating in elevated plasma levels of CRP.

The host immune response to invading pathogens is orchestrated by a complex network of cytokines and acute phase reactants that are mainly represented by, but are not limited to, the IL-6/CRP and IL-18/ferritin axes described above. Differences in several other cytokine plasma markers and APPs have been described in bacterial and viral infections (Tables 1 and 2). Particular interest has been raised for SAA, which is significantly increased in patients with bacterial infections as compared to patients with viral infections [44]. This increase positively correlates with circulating CRP levels, and some authors have considered SAA to be equivalent to CRP in clinical practice, although SAA might be a more sensitive marker in infections with low inflammatory activity [44]. Procalcitonin has emerged as a promising biomarker in infectious inflammation. The diagnostic accuracy of procalcitonin has proven superior to both CRP and SAA in the early identification of bacterial infections, and procalcitonin serves as

Table 1. Changes in plasma cytokine concentrations during infections.

	Bacterial Infection	Viral Infection
IL-1α	Low / N.D. [71]	N.D. [59]
IL-1β	Increased [71]	Increased [72]
IL-1Rα	Increased* [41]	Normal [41]
		N.D. [59]
IL-2	Increased* [41]	Increased [41]
IL-6	Increased* [41]	Low / ND [41, 59]
IL-18	Increased [73]	Increased [58, 59]
IFN-α	N.D. [74]	Increased† [59, 74]
IFN-γ	Increased [75, 76]	Increased [59]
TNF-α	Increased* [41, 71]	Normal [41]
		Increased [59, 72]

* Direct comparison between viral and bacterial infections revealed higher circulating levels in bacterial infections [41].

† Direct comparison between viral and bacterial infections revealed higher circulating levels in viral infections [74]. N.D.: not detected.

doi:10.1371/journal.ppat.1005973.t001

prognostic indicator for sepsis [61, 62]. The secretion of procalcitonin during these bacterial infections is stimulated by cytokine plasma markers such as IL-6 and tumor necrosis factor-α, whereas viral infections commonly attenuate the procalcitonin response, likely due to increased IFN-γ production [63, 64].

An interesting plasma inflammatory profile has been observed in macrophage activating syndrome (MAS). MAS comprises a heterogeneous group of life-threatening disorders featuring excessive activation of T cells and macrophages, leading to a cytokine storm. The development of MAS can be triggered by infectious diseases of viral or bacterial etiology and has been associated with exceptionally high serum levels of free IL-18 with concomitant hyperferritinemia, reflecting an IL-18/IL-18BP imbalance [65]. The circulating levels of IL-18 are remarkably high in both MAS and viral infections, even in comparison to severe bacterial sepsis. A likely explanation resides in the origin of circulating IL-18, with monocytes/macrophages being the

Table 2. Changes in circulating concentrations of acute phase proteins during infections.

	Viral and Bacterial Infections
CRP	Stimulated by both viral and bacterial infections, but reaches higher values during bacterial infections [44, 77, 78]
SAA	
Procalcitonin	
Ferritin	Elevated in viral infections [47, 56]
Retinol	Decreased during infections [79]
Haptogloblin	Not significantly different between neonates with and without an infection [80]
α1-antitrypsin	
LPS binding protein	Elevated in bacterial infections as compared to viral infections [68]
sTREM-1	
Neutrophil lipocalin	More elevated in bacterial infections as compared to viral infections [81]

CRP: C-reactive protein; SAA: serum amyloid A; sTREM-1: soluble triggering receptor expressed on myeloid cells-1.

doi:10.1371/journal.ppat.1005973.t002

main source of IL-18 in diseases of bacterial origin, while the largest amount of circulating IL-18 in MAS and viral diseases might originate from damaged endothelium. Anti-cytokine therapy using the IL-1 receptor antagonist anakinra provides a survival benefit for severe septic patients with features of MAS [66]. Because IL-1 has been shown to induce caspase-1 expression required for subsequent proteolytic maturation of pro-IL-18, anakinra can indirectly block the production of biologically active IL-18, thereby counteracting the overwhelming IL-18 response in septic patients with features of MAS [67].

Conclusions and Future Perspectives

The model we propose describes the pathophysiology underlying the distinct immune responses to bacterial and viral infections, thereby offering new incentives for future research. However, our model does not serve as direct diagnostic tool in clinical practice, because considerable controversy exists about the diagnostic benefit of CRP, and combining CRP with other circulating biomarkers (e.g., IL-6, IL-18, and procalcitonin) was found not to improve the prediction of microbiological etiology in patients with lower respiratory tract infection [68, 69]. This emphasizes the importance of using inflammatory plasma markers as integral part of the diagnostic armamentarium, in which the clinical picture and patient's history remain cornerstones. Further studies should elucidate the sensitivity and specificity of a plasma inflammatory signature consisting of IL-6, CRP, IL-18, and ferritin in distinguishing between viral and bacterial infections. It will also be important to assess the direct correlation between circulating concentrations of IL-18 and ferritin in viral infections, as current studies have only focused on either IL-18 or ferritin separately.

A large array of bacterial and viral infections should be investigated, as it may be expected that these two types of inflammatory reactions (IL-1/IL-6/CRP versus IL-18/ferritin) will not fully reflect the bacterial–viral infection dichotomy. In line with this, patients with influenza infection seem to have an inflammatory reaction more closely resembling a bacterial rather than viral infection [68], although this discrepancy might also be explained by an altered immune response due to (undetected) bacterial co-infection or the interference of influenza with caspase-1 activation [70]. More studies on various infections in larger cohorts are, thus, needed, and should also include fungal and parasitic infections.

References

1. Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nature immunology. 2004; 5(10):987–95. doi: 10.1038/ni1112 PMID: 15454922

2. Gruys E, Toussaint MJ, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins. Journal of Zhejiang University Science B. 2005; 6(11):1045–56. doi: 10.1631/jzus.2005.B1045 PMID: 16252337

3. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood. 2011; 117(14):3720–32. doi: 10.1182/blood-2010-07-273417 PMID: 21304099

4. Suwara MI, Green NJ, Borthwick LA, Mann J, Mayer-Barber KD, Barron L, et al. IL-1alpha released from damaged epithelial cells is sufficient and essential to trigger inflammatory responses in human lung fibroblasts. Mucosal immunology. 2014; 7(3):684–93. doi: 10.1038/mi.2013.87 PMID: 24172847

5. van de Veerdonk FL, Netea MG, Dinarello CA, Joosten LA. Inflammasome activation and IL-1beta and IL-18 processing during infection. Trends in immunology. 2011; 32(3):110–6. doi: 10.1016/j.it.2011.01.003 PMID: 21333600

6. Chaix J, Tessmer MS, Hoebe K, Fuseri N, Ryffel B, Dalod M, et al. Cutting edge: Priming of NK cells by IL-18. Journal of immunology. 2008; 181(3):1627–31.

7. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. Annual review of immunology. 2001; 19:423–74. doi: 10.1146/annurev.immunol.19.1.423 PMID: 11244043

8. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: an overview of signals, mechanisms and functions. Journal of leukocyte biology. 2004; 75(2):163–89. doi: 10.1189/jlb.0603252 PMID: 14525967

9. Ohtsuki T, Micallef MJ, Kohno K, Tanimoto T, Ikeda M, Kurimoto M. Interleukin 18 enhances Fas ligand expression and induces apoptosis in Fas-expressing human myelomonocytic KG-1 cells. Anticancer research. 1997; 17(5A):3253–8. PMID: 9413156

10. Napolitani G, Acosta-Rodriguez EV, Lanzavecchia A, Sallusto F. Prostaglandin E2 enhances Th17 responses via modulation of IL-17 and IFN-gamma production by memory CD4+ T cells. European journal of immunology. 2009; 39(5):1301–12. doi: 10.1002/eji.200838969 PMID: 19384872

11. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006; 441(7090):235–8. doi: 10.1038/nature04753 PMID: 16648838

12. Korn T, Mitsdoerffer M, Croxford AL, Awasthi A, Dardalhon VA, Galileos G, et al. IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105(47):18460–5. doi: 10.1073/pnas.0809850105 PMID: 19015529

13. Pasare C, Medzhitov R. Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. Science. 2003; 299(5609):1033–6. doi: 10.1126/science.1078231 PMID: 12532024

14. van de Veerdonk FL, Gresnigt MS, Kullberg BJ, van der Meer JW, Joosten LA, Netea MG. Th17 responses and host defense against microorganisms: an overview. BMB reports. 2009; 42(12):776–87. PMID: 20044948

15. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. The Journal of experimental medicine. 2006; 203(10):2271–9. doi: 10.1084/jem.20061308 PMID: 16982811

16. Hou W, Kang HS, Kim BS. Th17 cells enhance viral persistence and inhibit T cell cytotoxicity in a model of chronic virus infection. The Journal of experimental medicine. 2009; 206(2):313–28. doi: 10.1084/jem.20082030 PMID: 19204109

17. Colafrancesco S, Priori R, Alessandri C, Perricone C, Pendolino M, Picarelli G, et al. IL-18 Serum Level in Adult Onset Still's Disease: A Marker of Disease Activity. International journal of inflammation. 2012; 2012:156890. doi: 10.1155/2012/156890 PMID: 22762008

18. Shine B, de Beer FC, Pepys MB. Solid phase radioimmunoassays for human C-reactive protein. Clinica chimica acta; international journal of clinical chemistry. 1981; 117(1):13–23. PMID: 7333010

19. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. The Journal of clinical investigation. 1993; 91(4):1351–7. doi: 10.1172/JCI116336 PMID: 8473487

20. Crowell RE, Du Clos TW, Montoya G, Heaphy E, Mold C. C-reactive protein receptors on the human monocytic cell line U-937. Evidence for additional binding to Fc gamma RI. Journal of immunology. 1991; 147(10):3445–51.

21. Bharadwaj D, Stein MP, Volzer M, Mold C, Du Clos TW. The major receptor for C-reactive protein on leukocytes is fcgamma receptor II. The Journal of experimental medicine. 1999; 190(4):585–90. PMID: 10449529

22. Siegel J, Osmand AP, Wilson MF, Gewurz H. Interactions of C-reactive protein with the complement system. II. C-reactive protein-mediated consumption of complement by poly-L-lysine polymers and other polycations. The Journal of experimental medicine. 1975; 142(3):709–21. PMID: 809531

23. Mold C, Kingzette M, Gewurz H. C-reactive protein inhibits pneumococcal activation of the alternative pathway by increasing the interaction between factor H and C3b. Journal of immunology. 1984; 133(2):882–5.

24. Weiss G. Modification of iron regulation by the inflammatory response. Best practice & research Clinical haematology. 2005; 18(2):183–201.

25. Thomson AM, Rogers JT, Leedman PJ. Iron-regulatory proteins, iron-responsive elements and ferritin mRNA translation. The international journal of biochemistry & cell biology. 1999; 31(10):1139–52.

26. Cohen LA, Gutierrez L, Weiss A, Leichtmann-Bardoogo Y, Zhang DL, Crooks DR, et al. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. Blood. 2010; 116(9):1574–84. doi: 10.1182/blood-2009-11-253815 PMID: 20472835

27. Ghosh S, Hevi S, Chuck SL. Regulated secretion of glycosylated human ferritin from hepatocytes. Blood. 2004; 103(6):2369–76. doi: 10.1182/blood-2003-09-3050 PMID: 14615366

28. Tran TN, Eubanks SK, Schaffer KJ, Zhou CY, Linder MC. Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron. Blood. 1997; 90(12):4979–86. PMID: 9389717

29. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics: integrated biometal science. 2014; 6(4):748–73.

30. Broxmeyer HE, Williams DE, Geissler K, Hangoc G, Cooper S, Bicknell DC, et al. Suppressive effects in vivo of purified recombinant human H-subunit (acidic) ferritin on murine myelopoiesis. Blood. 1989; 73(1):74–9. PMID: 2910370

31. Fargion S, Fracanzani AL, Brando B, Arosio P, Levi S, Fiorelli G. Specific binding sites for H-ferritin on human lymphocytes: modulation during cellular proliferation and potential implication in cell growth control. Blood. 1991; 78(4):1056–61. PMID: 1831058

32. Broxmeyer HE, Lu L, Bicknell DC, Williams DE, Cooper S, Levi S, et al. The influence of purified recombinant human heavy-subunit and light-subunit ferritins on colony formation in vitro by granulocyte-macrophage and erythroid progenitor cells. Blood. 1986; 68(6):1257–63. PMID: 3490884

33. Gray CP, Arosio P, Hersey P. Heavy chain ferritin activates regulatory T cells by induction of changes in dendritic cells. Blood. 2002; 99(9):3326–34. PMID: 11964300

34. Li R, Luo C, Mines M, Zhang J, Fan GH. Chemokine CXCL12 induces binding of ferritin heavy chain to the chemokine receptor CXCR4, alters CXCR4 signaling, and induces phosphorylation and nuclear translocation of ferritin heavy chain. The Journal of biological chemistry. 2006; 281(49):37616–27. doi: 10.1074/jbc.M607266200 PMID: 17056593

35. Malle E, De Beer FC. Human serum amyloid A (SAA) protein: a prominent acute-phase reactant for clinical practice. European journal of clinical investigation. 1996; 26(6):427–35. PMID: 8817153

36. Shah C, Hari-Dass R, Raynes JG. Serum amyloid A is an innate immune opsonin for Gram-negative bacteria. Blood. 2006; 108(5):1751–7. doi: 10.1182/blood-2005-11-011932 PMID: 16735604

37. Song C, Hsu K, Yamen E, Yan W, Fock J, Witting PK, et al. Serum amyloid A induction of cytokines in monocytes/macrophages and lymphocytes. Atherosclerosis. 2009; 207(2):374–83. doi: 10.1016/j.atherosclerosis.2009.05.007 PMID: 19535079

38. Yamada T, Wada A, Itoh K, Igari J. Serum amyloid A secretion from monocytic leukaemia cell line THP-1 and cultured human peripheral monocytes. Scandinavian journal of immunology. 2000; 52(1):7–12. PMID: 10886778

39. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. British journal of pharmacology. 2010; 159(2):253–64. doi: 10.1111/j.1476-5381.2009.00433.x PMID: 20002097

40. Oberhoffer M, Karzai W, Meier-Hellmann A, Bogel D, Fassbinder J, Reinhart K. Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor-alpha and interleukin-6 in patients with sepsis. Critical care medicine. 1999; 27(9):1814–8. PMID: 10507603

41. Holub M, Lawrence DA, Andersen N, Davidova A, Beran O, Maresova V, et al. Cytokines and chemokines as biomarkers of community-acquired bacterial infection. Mediators of inflammation. 2013; 2013:190145. doi: 10.1155/2013/190145 PMID: 23690657

42. Yeung CY, Lee HC, Lin SP, Fang SB, Jiang CB, Huang FY, et al. Serum cytokines in differentiating between viral and bacterial enterocolitis. Annals of tropical paediatrics. 2004; 24(4):337–43. doi: 10.1179/027249304225019163 PMID: 15720891

43. Zarkesh M, Sedaghat F, Heidarzadeh A, Tabrizi M, Moghadam KB, Ghesmati S. Diagnostic Value of IL-6, CRP, WBC, and Absolute Neutrophil Count to Predict Serious Bacterial Infection in Febrile Infants. Acta Medica Iranica. 2015; 53(7).

44. Lannergard A, Larsson A, Kragsbjerg P, Friman G. Correlations between serum amyloid A protein and C-reactive protein in infectious diseases. Scandinavian journal of clinical and laboratory investigation. 2003; 63(4):267–72. PMID: 12940634

45. Custer EM, Finch CA, Sobel RE, Zettner A. Population norms for serum ferritin. The Journal of laboratory and clinical medicine. 1995; 126(1):88–94. PMID: 7602240

46. Kleiner G, Marcuzzi A, Zanin V, Monasta L, Zauli G. Cytokine levels in the serum of healthy subjects. Mediators of inflammation. 2013; 2013:434010. doi: 10.1155/2013/434010 PMID: 23533306

47. van de Veerdonk FL, Wever PC, Hermans MH, Fijnheer R, Joosten LA, van der Meer JW, et al. IL-18 serum concentration is markedly elevated in acute EBV infection and can serve as a marker for disease severity. The Journal of infectious diseases. 2012; 206(2):197–201. doi: 10.1093/infdis/jis335 PMID: 22689912

48. Vecchiet J, Falasca K, Cacciatore P, Zingariello P, Dalessandro M, Marinopiccoli M, et al. Association between plasma interleukin-18 levels and liver injury in chronic hepatitis C virus infection and non-alcoholic fatty liver disease. Annals of clinical and laboratory science. 2005; 35(4):415–22. PMID: 16254258

49. Stacey AR, Norris PJ, Qin L, Haygreen EA, Taylor E, Heitman J, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. Journal of virology. 2009; 83(8):3719–33. doi: 10.1128/JVI.01844-08 PMID: 19176632

50. Sharma A, Chakraborti A, Das A, Dhiman RK, Chawla Y. Elevation of interleukin-18 in chronic hepatitis C: implications for hepatitis C virus pathogenesis. Immunology. 2009; 128(1 Suppl):e514–22. doi: 10.1111/j.1365-2567.2008.03021.x PMID: 19740312

51. Wu J, Chen L, Chen Y, Yang J, Wu D. Serum ferritin concentration predicts mortality in patients with hepatitis B virus-related acute on chronic liver failure. Archives of medical research. 2014; 45(3):251–6. doi: 10.1016/j.arcmed.2014.03.004 PMID: 24656903

52. Stylianou E, Bjerkeli V, Yndestad A, Heggelund L, Waehre T, Damas JK, et al. Raised serum levels of interleukin-18 is associated with disease progression and may contribute to virological treatment failure in HIV-1-infected patients. Clinical and experimental immunology. 2003; 132(3):462–6. doi: 10.1046/j.1365-2249.2003.02179.x PMID: 12780693

53. Wiercinska-Drapalo A, Jaroszewicz J, Flisiak R, Prokopowicz D. Plasma interleukin-18 is associated with viral load and disease progression in HIV-1-infected patients. Microbes and infection / Institut Pasteur. 2004; 6(14):1273–7.

54. Riera A, Gimferrer E, Cadafalch J, Remacha A, Martin S. Prevalence of high serum and red cell ferritin levels in HIV-infected patients. Haematologica. 1994; 79(2):165–7. PMID: 8063264

55. Gupta S, Imam A, Licorish K. Serum ferritin in acquired immune deficiency syndrome. Journal of clinical & laboratory immunology. 1986; 20(1):11–3.

56. van de Weg CA, Huits RM, Pannuti CS, Brouns RM, van den Berg RW, van den Ham HJ, et al. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. PLoS Negl Trop Dis. 2014; 8(10):e3214. doi: 10.1371/journal.pntd.0003214 PMID: 25299654

57. Soundravally R, Agieshkumar B, Daisy M, Sherin J, Cleetus CC. Ferritin levels predict severe dengue. Infection. 2015; 43(1):13–9. doi: 10.1007/s15010-014-0683-4 PMID: 25354733

58. Mustafa AS, Elbishbishi EA, Agarwal R, Chaturvedi UC. Elevated levels of interleukin-13 and IL-18 in patients with dengue hemorrhagic fever. FEMS immunology and medical microbiology. 2001; 30 (3):229–33. PMID: 11335143

59. Michels M, de Mast Q, Netea MG, Joosten LA, Dinarello CA, Rudiman PI, et al. Normal free interleukin-18 (IL-18) plasma levels in dengue virus infection and the need to measure both total IL-18 and IL-18 binding protein levels. Clinical and vaccine immunology: CVI. 2015; 22(6):650–5. doi: 10.1128/CVI.00147-15 PMID: 25878254

60. Dinarello CA, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 binding protein. Frontiers in immunology. 2013; 4:289. doi: 10.3389/fimmu.2013.00289 PMID: 24115947

61. Jain S, Sinha S, Sharma SK, Samantaray JC, Aggrawal P, Vikram NK, et al. Procalcitonin as a prognostic marker for sepsis: a prospective observational study. BMC research notes. 2014; 7:458. doi: 10.1186/1756-0500-7-458 PMID: 25034373

62. Qu J, L X, Liu Y, Wang X. Evaluation of procalcitonin, C-reactive protein, interleukin-6 & serum amyloid A as diagnostic biomarkers of bacterial infection in febrile patients. The Indian journal of medical research. 2015; 141(3):315–21. PMID: 25963492

63. Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2011; 52 Suppl 4:S346–50.

64. Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. Annals of clinical biochemistry. 2001; 38(Pt 5):483–93. PMID: 11587126

65. Mazodier K, Marin V, Novick D, Farnarier C, Robitail S, Schleinitz N, et al. Severe imbalance of IL-18/IL-18BP in patients with secondary hemophagocytic syndrome. Blood. 2005; 106(10):3483–9. doi: 10.1182/blood-2005-05-1980 PMID: 16020503

66. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical care medicine. 2016; 44(2):275–81. doi: 10.1097/CCM.0000000000001402 PMID: 26584195

67. Toldo S, Mezzaroma E, O'Brien L, Marchetti C, Seropian IM, Voelkel NF, et al. Interleukin-18 mediates interleukin-1-induced cardiac dysfunction. American journal of physiology Heart and circulatory physiology. 2014; 306(7):H1025–31. doi: 10.1152/ajpheart.00795.2013 PMID: 24531812

68. ten Oever J, Tromp M, Bleeker-Rovers CP, Joosten LA, Netea MG, Pickkers P, et al. Combination of biomarkers for the discrimination between bacterial and viral lower respiratory tract infections. The Journal of infection. 2012; 65(6):490–5. doi: 10.1016/j.jinf.2012.08.004 PMID: 22898387

69. Salonen EM, Vaheri A. C-reactive protein in acute viral infections. Journal of medical virology. 1981; 8 (3):161–7. PMID: 6276502

70. Stasakova J, Ferko B, Kittel C, Sereinig S, Romanova J, Katinger H, et al. Influenza A mutant viruses with altered NS1 protein function provoke caspase-1 activation in primary human macrophages, resulting in fast apoptosis and release of high levels of interleukins 1beta and 18. The Journal of general virology. 2005; 86(Pt 1):185–95. doi: 10.1099/vir.0.80422-0 PMID: 15604446

71. Cannon JG, Tompkins RG, Gelfand JA, Michie HR, Stanford GG, van der Meer JW, et al. Circulating interleukin-1 and tumor necrosis factor in septic shock and experimental endotoxin fever. The Journal of infectious diseases. 1990; 161(1):79–84. PMID: 2295861

72. Giuffrida MJ, Valero N, Mosquera J, Alvarez de Mon M, Chacin B, Espina LM, et al. Increased cytokine/chemokines in serum from asthmatic and non-asthmatic patients with viral respiratory infection. Influenza and other respiratory viruses. 2014; 8(1):116–22. doi: 10.1111/irv.12155 PMID: 23962134

73. Tschoeke SK, Oberholzer A, Moldawer LL. Interleukin-18: a novel prognostic cytokine in bacteria-induced sepsis. Critical care medicine. 2006; 34(4):1225–33. doi: 10.1097/01.CCM.0000208356.05575.16 PMID: 16540967

74. Mangiarotti P, Moulin F, Palmer P, Ravilly S, Raymond J, Gendrel D. Interferon-alpha in viral and bacterial gastroenteritis: a comparison with C-reactive protein and interleukin-6. Acta paediatrica. 1999; 88(6):592–4. PMID: 10419239

75. Stoycheva M, Murdjeva M. Serum levels of interferon-gamma, interleukin-12, tumour necrosis factor-alpha, and interleukin-10, and bacterial clearance in patients with gastroenteric Salmonella infection. Scandinavian journal of infectious diseases. 2005; 37(1):11–4. PMID: 15764184

76. Katti MK. Assessment of serum IL-1, IL-2 and IFN-gamma levels in untreated pulmonary tuberculosis patients: role in pathogenesis. Archives of medical research. 2011; 42(3):199–201. doi: 10.1016/j.arcmed.2011.04.012 PMID: 21722815

77. Nakayama T, Sonoda S, Urano T, Yamada T, Okada M. Monitoring both serum amyloid protein A and C-reactive protein as inflammatory markers in infectious diseases. Clinical chemistry. 1993; 39 (2):293–7. PMID: 8381732

78. Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guerin S, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. The Pediatric infectious disease journal. 1999; 18(10):875–81. PMID: 10530583

79. Thurnham DI, McCabe GP, Northrop-Clewes CA, Nestel P. Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A deficiency: meta-analysis. Lancet. 2003; 362(9401):2052–8. PMID: 14697804

80. Speer C, Bruns A, Gahr M. Sequential determination of CRP, alpha 1-antitrypsin and haptoglobin in neonatal septicaemia. Acta paediatrica Scandinavica. 1983; 72(5):679–83. PMID: 6416019

81. Venge P, Douhan-Hakansson L, Garwicz D, Peterson C, Xu S, Pauksen K. Human Neutrophil Lipocalin as a Superior Diagnostic Means To Distinguish between Acute Bacterial and Viral Infections. Clinical and vaccine immunology: CVI. 2015; 22(9):1025–32. doi: 10.1128/CVI.00347-15 PMID: 26135974

82. Netea MG, Kullberg BJ, Van der Meer JW. Circulating cytokines as mediators of fever. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2000; 31 Suppl 5: S178–84.

83. Bradley JR. TNF-mediated inflammatory disease. The Journal of pathology. 2008; 214(2):149–60. doi: 10.1002/path.2287 PMID: 18161752

84. Wang X, Feuerstein GZ, Gu JL, Lysko PG, Yue TL. Interleukin-1 beta induces expression of adhesion molecules in human vascular smooth muscle cells and enhances adhesion of leukocytes to smooth muscle cells. Atherosclerosis. 1995; 115(1):89–98. PMID: 7545398

85. Andoh A, Takaya H, Saotome T, Shimada M, Hata K, Araki Y, et al. Cytokine regulation of chemokine (IL-8, MCP-1, and RANTES) gene expression in human pancreatic periacinar myofibroblasts. Gastroenterology. 2000; 119(1):211–9. PMID: 10889171

86. Hollenberg SM, Cunnion RE, Parrillo JE. The effect of tumor necrosis factor on vascular smooth muscle. In vitro studies using rat aortic rings. Chest. 1991; 100(4):1133–7. PMID: 1914573

87. Hofmann S, Grasberger H, Jung P, Bidlingmaier M, Vlotides J, Janssen OE, et al. The tumour necrosis factor-alpha induced vascular permeability is associated with a reduction of VE-cadherin expression. European journal of medical research. 2002; 7(4):171–6. PMID: 12010652

88. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature. 2001; 410 (6827):471–5. doi: 10.1038/35068566 PMID: 11260714

89. Tosato G, Jones KD. Interleukin-1 induces interleukin-6 production in peripheral blood monocytes. Blood. 1990; 75(6):1305–10. PMID: 2310829

90. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. The New England journal of medicine. 1999; 340(6):448–54. doi: 10.1056/NEJM199902113400607 PMID: 9971870

91. Falasca K, Ucciferri C, Dalessandro M, Zingariello P, Mancino P, Petrarca C, et al. Cytokine patterns correlate with liver damage in patients with chronic hepatitis B and C. Annals of clinical and laboratory science. 2006; 36(2):144–50. PMID: 16682509

92. Lau B, Sharrett AR, Kingsley LA, Post W, Palella FJ, Visscher B, et al. C-reactive protein is a marker for human immunodeficiency virus disease progression. Archives of internal medicine. 2006; 166 (1):64–70. doi: 10.1001/archinte.166.1.64 PMID: 16401812

93. Chen CC, Lee IK, Liu JW, Huang SY, Wang L. Utility of C-Reactive Protein Levels for Early Prediction of Dengue Severity in Adults. BioMed research international. 2015; 2015:936062. doi: 10.1155/2015/936062 PMID: 26247033

94. Skowronski M, Zozulinska-Ziolkiewicz D, Juszczyk J, Michalski W, Wierusz-Wysocka B. C-reactive protein and chronic hepatitis C virus infection in diabetic patients. Polskie Archiwum Medycyny Wewnetrznej. 2010; 120(12):491–6. PMID: 21178905

95. Thanoon I, Khlaf M, Oglah M. Assessment of C-Reactive Protein and Oxidative/Antioxidative Status in Children with Acute Bacterial Meningitis. Malaysian Journal Pharmaceutical Sciences. 2009; 7 (1):2009.

96. Shanbhogue LK, Paterson N. Effect of sepsis and surgery on trace minerals. JPEN Journal of parenteral and enteral nutrition. 1990; 14(3):287–9. PMID: 2352339

97. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Critical care. 2004; 8(4):R234–42. doi: 10.1186/cc2877 PMID: 15312223

98. Darton TC, Blohmke CJ, Giannoulatou E, Waddington CS, Jones C, Sturges P, et al. Rapidly Escalating Hepcidin and Associated Serum Iron Starvation Are Features of the Acute Response to Typhoid Infection in Humans. PLoS neglected tropical diseases. 2015; 9(9):e0004029. doi: 10.1371/journal.pntd.0004029 PMID: 26394303

99. Garcia PC, Longhi F, Branco RG, Piva JP, Lacks D, Tasker RC. Ferritin levels in children with severe sepsis and septic shock. Acta paediatrica. 2007; 96(12):1829–31. doi: 10.1111/j.1651-2227.2007.00564.x PMID: 18001337

100. Fioretto JR, Martin JG, Kurokawa CS, Carpi MF, Bonatto RC, de Moraes MA, et al. Comparison between procalcitonin and C-reactive protein for early diagnosis of children with sepsis or septic shock. Inflammation research: official journal of the European Histamine Research Society [et al]. 2010; 59(8):581–6.