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REVIEW ARTICLE

INFLAMMATORY MARKERS IN INFECTIOUS DISEASES – AN UPDATE

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Abstract

A host of acute phase proteins whose concentrations increase in blood following infection or inflammations are called inflammatory markers. Hundreds of such markers have been identifiedin various infection diseases, but only very few are being measured by clinical laboratories for diagnostic purpose. While established assays for inflammatory markers like hsCRP, Immunoglobins, procalcitonin, TNF-α, α-1 antitrypsin, haptoglobins and some interleukins such as IL-6 are available, studies are underway to make other established inflammatory markers for diagnostic use. This paper brings out an update on many inflammatory markers produced by varieties of pathogens such as viruses and bacteria. The contents of this paper will make awareness among researchers and biomedical scientists to develop assays for better diagnosis/management of varieties of diseases produced by a host of pathogens.
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Keywords: C-reactive protein, Cytokines, Interleukins, Tumor necrosis factor, Interferons, Procalcitonin.

Introduction

Every infectious diseases is accompanied by the release of one or more inflammatory markers. The most common infectious diseases identified and possible diagnostic and treatment options available are; Trypanosomiasis, Chlorea, Cryptospondosis, Dengue, Hepatitis, Hepatitis B, Japanese Encephalitis, Leishmania, Onchocerciasis, Rotavirus and Bacteria. Further many inflammatory markers have been identified in such diseases, both in humans and animals. This paper is an attempt to bring out an uptodate inflammatory markers identified so far and its diagnostic significance. The various inflammatory markers identified during the last two decades in varieties of diseases listed above are summarised below.

TRYPANOSOMIASIS

Acetyl Choline Esterase (AChE) and Butyryl Choline Esterase (BChE) are pro -inflammatory markers, both of which reduce the concentration of acetylcholine, a neurotransmitter which has an anti-inflammatory property.[1]Seropositive patients had prolonged QRS, decreased ejection fraction and high serum magnesium, all of which are useful in the diagnosis ofHeart Failure (HF) seronegative cases. Although C Reactive Protein (CRP), interleukin-6 (IL-6), interleukin- β1(IL-β1), interleukin-2 (IL-2), and factor de necrosis tumoral alfa (FNTα)are elevated in HF patients, only IL-2 levels are associated with chagasic HF.[2]The increased knowledge of lipid bodies in pathogenic mechanisms of infections may not only contribute to the understanding of pathogen-host interactions but may also identify new targets for intervention.[3]Meningo-encephalitic state of human african trypanosomiasis denutrition was a major biological and clinical feature in association with lymphoid cells stimulation as revealed by beta 2 microglobulins levels.[4]A positive correlation

observed between inflammatory infiltrates and CK-MB levels suggests that CK-MB could be useful to monitor the occurrence of experimental chagasic myocarditis.[5]No statistically significant difference was observed for IgA, IgM or IgG levels among T. cruzi infected animals. However, IgA together IgM levels have shown to be good markers for the acute phase of Chagas disease.[6]

T. cruzi infection and endothelin-1 (ET-1) cooperatively activated the Ca(2+)/calcineurin (Cn)/nuclear factor of activated T cells (NFAT) signaling pathway in atrial myocytes, leading to cyclooxygenase-2 (COX-2) protein expression and increased eicosanoid (prostaglandins E(2) and F(2α), thromboxane A(2)) release. T. cruzi infection of ET-1-stimulated cardiomyocytes resulted in significantly enhanced production of atrial natriuretic peptide, a prognostic marker for impairment in cardiac function of chagasic patients. A role for the Ca(2+)/Cn/NFAT cascade in T. cruzi-mediated myocardial production of inflammatory mediators may help define novel therapeutic targets.[7]Fas/Fas-L (Fas ligand) engagement is necessary for regulated and physiological apoptosis in a number of systems. Although Fas signals have become inextricably associated to cell death, it is now clear that Fas-triggering induces cellular and immunological responses far beyond its relevance in apoptosis. Fas can induce cell activation, proliferation, differentiation, secretion of cytokines, chemokines, recruitment of inflammatory cells, cell survival and more.[8]

CHOLERA

Innate arm may be important in the host's defence against cholera. Such effects may need to be simulated in a vaccine to achieve long lasting protection from cholera.[9]Chronic inflammation and nerve injury may share some common mechanisms in generating allodynia and hyperalgesia.[10]Cholera toxin stimulated the release of Tumor necrosis factor alpha (TNF-α) by macrophages and hence cholera toxin exhibits significant pro-inflammatory activity. It also indicates the role of TNF-α on the pathophysiology of cholera toxin based on the inhibitory action of dexamethasone (DEXA), thalidomide (TAL) and pentoxifylline, and on TNF-α secretion.[11]Neutrophils impact disease progression suggest that neutrophil effectiveness can be manipulated through the deletion of accessory toxins.[12]Extracellular nuclease production by*Vibrio (V).Cholera* may enhance survival fitness of the pathogen through Neutrophil extracellular trap degradation.[13]Increases in the levels of gut-homing T and B cells, as well as involvement of CD8 and CD4 Th1-mediatedinterferon and CD4 Th2-mediated IL-13 cytokine responses may take place in acute dehydrating disease caused by *V. Cholerae* O1 and studies are needed to determine if such responses are also stimulated after immunization with oral cholera vaccines and if these responses play a role in protection following exposure to cholera.[14]

The levels of nonspecific mediators of the innate defense system, prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4), and lactoferrin (Lf), as well as myeloperoxidase (MPO), were elevated at the acute stage of the disease in stools obtained from both O1- and O139-infected adults and children. In the systemic compartment, the levels of Lf were increased after onset of disease, which in children remained elevated up toconvalescence compared to the healthy controls. Elevated concentrations of Lf, MPO, PGE_2, LTB_4, and Nitric Oxide (NO), as well as other metabolites during the acute stage of the disease indicate that the innate defense system, as well as the inflammatory process is activated in both adults and pediatric patients infected with*V. Cholerae* O1 and O139.[15]*V.Cholerae* is the causal intestinal pathogen of the diarrheal disease cholera. It secretes the protease PrtV, which protects the bacterium from invertebrate predators but reduces the ability of *Vibrio*-secreted factor(s) to induce interleukin-8 (IL-8) production by human intestinal epithelial cells.[16]Susceptibility to *V. cholerae* infection is determined by a combination of immunologic, nutritional, and genetic characteristics; additional factors that influence susceptibility to cholera remain unidentified.[17] The innate immune response impacts the colonization of *V. cholerae* in vivo.It is postulated that extracellular nuclease production *by V. cholerae* may enhance survival fitness of the pathogen through *Neutrophil Extracellular Trap (NET)* degradation.[18]

CRYPTOSPORIDIOSIS

The mechanisms by which Cryptosporidium (C) parvum cause persistent diarrhea and increased morbidity and mortality are poorly understood. Markers of a proinflammatory immune response, IL-8 and TNFα receptor, were significantly elevated in

the case population as was fecal lactoferrin and the T helper (Th)-2 cytokine IL-13. The counterregulatory cytokine IL-10 was exclusively elevated in the case population.A Th1 cytokine response to infection was not detected. Triple cohort study demonstrates that malnourished children with acute cryptosporidiosis mount inflammatory, Th-2, and counterregulatory intestinal immune responses.[19]In malnourished children, persistent diarrhea is associated with increased susceptibility to recurrent diarrheal episodes, which can lead to death or chronic nutritional and cognitive sequelae.The host immune response plays a critical role in the control of human cryptosporidiosis. The immune cells in the peripheral blood may exhibit properties different from the properties of cells found in the intestinal compartment. Knowledge about the human immune response towards C infection is far from complete but some recent advances have been made.[20]

Although $CD4^+$ T cells may be important for elimination of *C. parvum*, these cells are dispensable for controlling the early acute phase of infection in neonates.[21] apoE plays a key role in the intestinal restitution and immunoinflammatory responses with C infection and malnutrition.[22]Immune responses play a critical role in protection from, and resolution of, cryptosporidiosis. However, the nature of these responses, particularly in humans, is not completely understood. Innate immune responses may be mediated by Toll-like receptor pathways, antimicrobial peptides, prostaglandins, mannose-binding lectin, cytokines and chemokines.[23]*C*infection can cause undernutrition and, conversely, that weanling undernutrition intensifies infection and mucosal damage.[24]C was associated with increased levels of IL-8 and TNF-α systemically, which persisted at 6 months after enrollment. The level of intestinal TNF-α was elevated at enrollment, but elevated levels did not persist. Worsening of malnutrition, particularly stunting, was observed after infection. The association of C inflammation and stunting in children with C warrants further evaluation.[25]

DENGUE

Dengue fever is one of the most significant re-emerging tropical diseases, despite our expanding knowledge of the disease, viral tropism is still not known to target heart tissues or muscle. Derangements of Ca2+ storage in the infected cells may directly contribute to the presentation of myocarditis in pediatric patients.[26]The systemic host inflammatory and coagulation activation response occurs early in patients with dengue viral infection in the absence of severe hemorrhagic manifestations, and provides the basis for considering future clinical study in the use of recombinant human activated protein C to treat patients with severe sepsis from dengue infection.[27]Dengue shock syndrome patients had significantly higher levels of IL-6 and Secretory phospholipase A2 (SPLA2)than normotensive patients associated with a higher incidence of ascites. CRP concentrations in dengue patients and in healthy children were not different, but lower than in children with bacterial infections. That IL-6 and sPLA2 may have a pathogenetic role only in the most severe forms of dengue virus infection.[28]Dengue shock syndrome is a severe complication of dengue hemorrhagic fever (DHF), characterized by a massive increase in vascular permeability. Large-scale release of soluble Tumor Necrosis Factor –R (TNFR) may be an early and specific marker of the endothelial changes that cause dengue shock syndrome.[29]Significant differences in expression of the cytokines were seen between the dengue immune profiles, suggesting that the sequence in which the immune system encounters serotypes may be important in determining the nature of the immune response to subsequent infections.[30]IL-8 levels are increased in most patients with dengue virus infection and correlate with degranulation of neutrophils as well as with some clinical and hemodynamic variables,suggesting a role for IL-8 in the pathogenesis of dengue virus infection.[31]Several studies have shown that serum IL-10, IFNγ and Macrophage migration inhibitory factor (MIF) are elevated in patients with severe dengue (SD) and could be used as potential biomarkers. Although serum IL-10 was significantly elevated in patients with SD, it had a poor discriminatory value in identifying those with SD and non SD and therefore, is unsuitable to be used as a robust biomarker in this cohort.[32]

HEPATITIS

Lymphadenopathy reflects ongoing hepatic inflammation in prolonged cholestatic hepatitis A.[33]Sinusoidal lining cells in Hepatitis C Viruses(HCV) biopsies and non-HCV biopsies with inflammation expressed Human Leukocyte

Antigen–DR (HLA-DR), intercellular adhesion molecule (ICAM-1) and CD4 and Transforming Factor – β (TGF-β) was increased in foci of necrosis. Inflammation in chronic HCV involves common immune-mediated cellular effector pathways and the inflammation in the portal triads represents aggregation of both T and B cells, mediated in part by upregulation of adhesion molecules on portal stromal cells suggesting response to antigensdraining from necroinflammato ry foci in the lobules. TGF-β is increased in active necroinflammatory foci, but not in portal lymphoid aggregates.[34]Pretreatment Chemokine CXCL10 levels were significantly higher in patients without an early virological response (EVR) or sustained virological response (SVR) compared to responders. Pretreatment plasma levels of the other soluble inflammatory markers evaluated were not associated with a treatment response. Pretreatment CXCL10 levels were predictive of both EVR and SVR to IFN-α and ribavirin and may be useful in the evaluation of candidates for therapy.[35]Effective treatment with a direct-acting antiviral agent may reduce hepatic inflammation and that first-phase HCV RNA decline during treatment with an NS3/4A protease inhibitor is more robust in patients with high baseline IP-10 concentrations.[36].

Chemokines might be used to monitor the natural course and progression of HCV-associated liver disease, to identify patients with a high likelihood of achieving a therapeutic response, and they may even have potential as therapeutic targets.[37]High levels of profibrinogenic cytokine TGF-β, metalloprotease (MMP2), and tissue inhibitor of matrix metalloprotease 1 (TIMP1) contribute to fibrogenesis in HCV infection and in alcohol-induced liver disease (ALD). Both TNF-α and TGF-β levels are increased significantly with the severity of inflammation and fibrosis. TGF-β levels increased significantly in ALD patients compared to HCV patients. Proinflammatory cytokines responses to viral and/or toxic injury differed with the severity of liver inflammation. A combination of these markers was useful in predicting and diagnosing the stages of inflammation and fibrosis in HCV and ALD. Therapeutic monitoring of TGF-β and metalloproteases provides important insights into fibrosis.[38]After controlling for the confounders, HCV was not associated with metabolic syndrome but associated with Homeostasis Model Assessment (HOMA) of insulin resistance and inflammatory marker ferritin. Among subjects with both HCV and metabolic syndrome, the adjusted HOMA insulin level was higher than those without HCV and metabolic syndrome. In addition, the serum ferritin level was a strong predictor of HOMA insulin resistance. In clinical practice, serum ferritin can be obtained along with routine blood tests in any laboratory, and it has a potential to be a surrogate marker of insulin resistance in people with HCV and metabolic syndrome.[39]

After adjustment for demographic and clinical factors, HCV remained significantly associated with an increased risk for Coronary Heart Disease (CHD) and HCV seropositive CHD patients had higher rates of death. After adjustment for Cardio Vascular Disease(CVD) risk factors, HCV seropositivity remained independently associated with risk for HF events.[40]Serum basement membrane peptides are accurate non-invasive markers of liver fibrosis and liver inflammation in chronic hepatitis C (CHC). These markers are superior to serum Alanine Transaminase (ALT) in reflecting liver injury and they have high specificity and sensitivity in detecting advanced liver disease in CHC.[41] Serum markers of hepatic inflammation and fibrosis are overexpressed in HIV-HCV-coinfected patients with advanced immunosuppression, while highly active antiretroviral therapy (HAART) has a "protective" effect.[42]With regard to necroinflammatory activity, AST,GGT and ALP werethe best markers to differentiate mild and severe activity. In HCV Hepatosplenic Schistosomiasis (HSS) patients, total bilirubin was capable of differentiating between mild and severe fibrosis. It is a biological marker that is non-invasive candidate toevaluate fibrosis and necroinflammatory activity in HCV and HCV + HSS.[43]

Monitoring ofVCAM-1 and hyaluronic acid during antiviral therapy does not differentiate between responders and non-responders. A decrease in ICAM-1 levels during IFN + ribavirin treatment is associated with response to therapy, and its efficacy in predicting long-term response should be further substantiated.[44]The inhibition of High-mobility group box 1 (HMGB1) may reduce inflammation, apoptosis and fibrosis, and may stop the progression of chronic liver disease. Fibrotic progression in chronic liver patients may be prevented by the inhibition of HMGB1, and that this substance can be a new means of following chronic

HBV treatment.[45]Effective treatment with a direct-acting antiviral agent may reduce hepatic inflammation and that first-phase HCV RNA decline during treatment with an NS3/4A protease inhibitor is more robust in patients with high baseline IP-10 concentrations.[46]

HEPATITIS B

In inflammatory bowel disease (IBD) patients, multivariate analysis in patients less than 30 years was an independent risk factor for nonimmune status.IBD was not a risk factor for HBV infection even in endemic areas. However, many young IBD patients were susceptible to HBV infection. It is crucial to screen for HBV immunity and to implement a meticulous vaccination strategy for IBD patients.[47]The best model for predicting significant inflammation included the variables age, HBV DNA levels, AST, and albumin. In HBeAg positive patients no factor could predict accurately stages of liver fibrosis, but the best factor for predicting significant inflammation was AST. Significant hepatic fibrosis and necroinflammation can reliably be predicted using routinely checked tests and HBV DNA levels.[48]Hepatitis C is an important burden worldwide being an important cause of cirrhosis and liver cancer in different parts of the world. Host immune response, especially Th1 cell-mediated, seems to play an important role in disease progression but is also crucial for viral elimination following specific therapy. Immune activation can be evaluated using peripheral levels of different cytokines, such as different chemokines (e.g. CCL5, CXCL10) and TNF-α, and their soluble receptors TNF-αreceptors 1(sTNF-R1) and 2 (sTNF-R2).[49]

All IBD patients should be screened for HBV markers at diagnosis and those who are positive for the hepatitis B surface antigen(HbsAg) should receive antiviral prophylaxis before undergoing immunosuppression in order to avoid HBV reactivation. Tenofovir/entecavir are preferred to lamivudine as nucleos(t)ide analogues due to their better resistance profile. In patients with occult or resolved HBV, viral reactivation does not appear to be a relevant issue and regular DNA determination is recommended during immunosuppression therapy. Consensus guidelines on this topic have been published in recent years for prevention and management of HBV infection in IBD patients.[50]Apolipoprotein A-I presents heterogeneous change in expression level with different isoforms and alpha1-antitrypsin produces evidently different fragments implying diverse cleavage pathways. These unique phenomena appear specific to HBV infection. A combination simultaneously considering the quantities and isoforms of these proteins could be a useful serum biomarker (or index) for HBV diagnosis and therapy.[51]No definite HBV reactivations were found in anti-HBc positive patients lacking HBsAg.Liver dysfunction in patients with IBD treated with immunosuppressants is more frequent and severe in those with HBV than in HCV carriers and is associated with combined immunosuppression.[52]Autoimmune hepatitis (AIH) is a chronic necroinflammatory disease of the liver characterized by hypergammaglobulinemia, characteristic autoantibodies, association with HLA DR3 or DR4 and a favorable response to immunosuppressive treatment, but the etiology is unknown.[53]

JAPANESE ENCEPHALITIS

Despite the availability of effective vaccines, Japanese encephalitis virus (JEV) infections remain a leading cause of encephalitis in many Asian countries. The virus is transmitted to humans by *Culex* mosquitoes, and, while the majority of human infections are asymptomatic, up to 30% of JEV cases die and 50% of the survivors suffer from neurological sequelae. Microglia are brain-resident macrophages that play key roles in both the innate and adaptive immune responses in the Central Nervous System(CNS) and are important in determining the pathology of encephalitis as a result of JEV infection.[54]CytokinesTNF-α and IL-2, are small secreted proteins, which mediate and regulate immunity. TNF-α pathway is involved in JEV infection-triggered neuroinflammation.[55]JEV is a flavivirus generated dreadful CNS disease which causes high mortality in various pediatric groups. JEV disease is currently diagnosed by measuring the level of viral antigens and virus neutralization of IgM antibodies in blood serum and CSF by ELISA. There is an utmost need for the development of new more authentic, appropriate, and reliable physiological, immunological, biochemical, biophysical, molecular and therapeutic biomarkers to confirm the disease well in time to start the clinical aid to the patients.[56]

An infectious encephalitis may also be difficult to distinguish from an encephalopathy that may be associated with numerous metabolic causes. Among the factors which have helped to focus

attention on viral encephalitis over the last few years have been the development of effective antiviral agents for this condition, most notably acyclovir for herpes simplex virus encephalitis (HSE).[57]The emergence of unusual forms of zoonotic encephalitis has posed an important public health problem. Vaccination and vector control measures are useful preventive strategies in certain arboviral and zoonotic encephalitis. However, we need better antiviral therapy to meet the challenge of acute viral encephalitis more effectively.[58]JEV infection is a major cause of acute encephalopathy in children, which destroys CNS cells, including astrocytes and neurons. Matrix metalloproteinase (MMP-9) has been shown to degrade components of the basal lamina, leading to disruption of the blood-brain barrier (BBB) and to contribute to neuroinflammatory responses in many neurological diseases. However, the detailed mechanisms of JEV-induced MMP-9 expression in rat brain astrocytes (RBA-1 cells) are largely unclear. JEV activates the ROS/c-Src/PDGFR/PI3K/Akt/MAPKs pathway, which in turn triggers AP-1 activation and ultimately induces MMP-9 expression in RBA-1 cells. These findings concerning JEV-induced MMP-9 expression in RBA-1 cells imply that JEV might play an important role in CNS inflammation and diseases.[59]

LEISHMANIA

Leishmania (L) major is a strong inducer of the early inflammatory response, compared with *L. donovani, an*d suggest that such an immunologic event potentially could restrain this parasite to the inoculation site, favoring the development of local swelling and cutaneous lesions.[60]As the malaria sera contained IgG anti-IgE antibodies, such complexes probably also play a role in the induction of TNF in vivo. Overproduction of TNF is considered a major pathogenic mechanism responsible for fever and tissue lesions in P. falciparum malaria. This overproduction is generally assumed to reflect a direct stimulation of effector cells by certain parasite-derived toxins. IgE elevation constitutes yet another important mechanism involved in excessive TNF induction in this disease.[61]Glycosylphosphatidylinositol (GPI)s are degraded by the macrophage surface phospholipases predominantly into inactive species, indicating that the host can regulate GPI activity at least in part by this mechanism and hence macrophage surface phospholipases play important roles in the GPI-induced innate immune responses and malaria pathogenesis.[62]The measles virus genome was found in none of the intestinal biopsies. Endothelial cell autoantibodies are not a genetic but rather an epigenetic (infectious) marker of disease susceptibility. The expression of these autoantibodies is unlikely to be triggered by a persistent measles virus infection.[63]

Measuring the current levels of antibodies specific for such viruses is useful for determining whether patients have seropositive antibody levels before immunomodulators/biologics are used for therapy.[64]The sequences obtained from patients with Crohn's disease and ulcerative colitis and children with autism were consistent with being vaccine strains, and the results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in peripheral mononuclear cells (PBMC) in some patients with chronic intestinal inflammation.[65]Clinicians must remain keenly appreciative of subtle shades of grey: acute disseminated encephalomyelitis (ADEM), first multiple sclerosis relapse, or ultimately benign clinically isolated syndrome? The answers are relevant to prognosis and, more recently, selection of the correct therapeutic strategy.[66]Changes in the concentrations of serum amyloid protein A (SAA) paralleled those in serum CRP in bacterial infection; during the course of viral infection, however, serum SAA tended to disappear more quickly than CRP did. SAA appears to be a clinically useful marker of inflammation in acute viral infections, with or without significant changes in the CRP concentration.[67]

ONCHOCERCIASIS

A considerable increase of elastase levels after treatment was observed, whereas lactoferrin levels did not change. The percentage of patients with elevated elastase levels was significantly correlated with the degree of side effects suggesting that neutrophil activation may be involved in the development of adverse reactions in these patients.[68]Mast cells play a role in initiation of tissue inflammatory reactions after ivermectin treatment of onchocerciasis.[69]There were no differences in the rates of parasite recovery in Erythropoietin (EPO) deficient mice and wild-type mice. Immunity did not develop in the μMT mice but did develop in the Xid miceand protective immunity was abolished in mice treated to eliminate IgE from the blood. IgE and eosinophils are required for adaptive protective immunity to larval *O. volvulus* in

mice.[70]Circulating levels of microbial translocation products (lipopolysaccharide and LPS-binding protein), acute phase proteins (haptoglobin and serum amyloid protein-A), and inflammatory cytokines (IL-1β, IL-12, and TNF-α) are associated with pathogenesis of disease in lymphatic filarial infection and implicate an important role for circulating microbial products and acute phase proteins.[71]

The presence of eosinophil-derived proteins in luminal secretions is reflective of mucosal inflammation in children with eosinophilic oesophagitis (EoE). The oesophageal string test (EST) is a novel, minimally invasive device for measuring oesophageal eosinophilic inflammation in children with EoE.[72]Significant correlations were also seen between *Wolbachia* DNA and the antibacterial peptides calprotectin and calgranulin B . These findings support a role for *Wolbachia* products in mediating the inflammatory responses seen following treatment of onchocerciasis and suggest new targets for modulating these reactions.[73] Concomitant findings of lymphocyte infiltration and resident cell activation indicate a dynamic state of localized host responsiveness presumably due to the microfilarial parasites and their products in the anterior segments of the eyes of patients with ocular onchocerciasis.[74]Onchocerca volvulus (Ov)Ov20/–OvS1 appears a promising candidate antigen for the diagnosis of onchocerciasis and in particular for the detection of the sowda type of disease.[75]

The levels of plasma IL-6 concentration declined significantly with time in the prone position ventilation(PRONE) group. The levels of plasma IL-6 concentration at enrolment, 24 hours and 72 hours after enrolment also predicted the 14th day mortality of all patients. PRONE was a safe and effective maneuver for improving oxygenation in patients with severe community-acquired pneumonia (CAP) and Acute respiratory distress syndrome (ARDS). PRONE also influenced IL-6 expression in patients with severe CAP.[76]There was also a strong correlation between the chest X ray reading of alveolar pneumonia with the inflammatory markers of CRP and leucocyte values. Inflammatory markers such as CRP, leucocytes and chest X rays are used in evaluating the severity of pneumonia.[77]Bacterial infections were associated with higher CRP than viral infections. Receiver operating characteristic curve of the model for differentiating bacterial from viral pneumonia are based on age, CRP, and neutrophil count produced area. This aetiological discriminant prediction model is a potentially useful tool in clinical management and epidemiological studies of paediatric pneumonia.[78]

ROTAVIRUS& BACTERIA

These intestinal infection-induced plasmablasts lack the cutaneous lymphocyte antigen (CLA) homing receptor for skin, consistent with mechanisms of differential CCR10 participation in skin T versus intestinal plasma cell homing. Interestingly, RV memory cells generally lack CCR9 and CCR10 and instead express CCR6, which may enable recruitment to diverse epithelial sites of inflammation.[79]An efficient entry of non-replicative rotavirus virus-like particles (VLP) into the epithelial cell line MA104 and provide the first in vivo evidence of the potential of these nanoparticles as a promising safe candidate for drug delivery to intestinal cells.[80]Mean platelet volume (MPV) could be used as an acute phase reactant in children with rotavirus gastroenteritis.[81]

Plasmacytoid DCs (pDC) -dependent antibody production influences viral clearance and mucosal pDCs critically influence the course of rotavirus infection and subsequent IFN production and display powerful adjuvant properties to initiate and enhance humoral immunity.[82]Elevated levels of TNFα, IL-1*β*, IL-6, and IL-10 were detected in faeces and in gut segments from infected animals. Bacteria were present inside epithelial cells and within colonic lamina propria. In contrast, an isogenic strain lacking Shiga toxin induced similar but milder symptoms, with moderate mucosal damage and lower cytokine levels.[83]In accordance with the histological findings, cytokine production was also upregulated during the convalescent phase; there was no significant difference in the incidence of cytokine-producing cells between acute (2 to 8 days after the onset of diarrhea) and convalescent (30 days after onset) stages.[84]Acute shigellosis elicits an acute phase response, the magnitude of which predicts clinical outcome.[85]Measurement of stool TNFα concentrations may provide a simple way to monitor disease activity in inflammatory bowel disease.[86]Whether inflammatory markers such as CRP, white Blood cell count (WBC) and PCT can differentiate streptococcal from viral tonsillitis should be investigated further.[87]

The clinical bottom line is that WBC, CRP and PCT levels are higher in patients with streptococcal tonsillitis compared to patients with tonsillitis or pharyngitis without group A streptococcus isolated from a throat swab. Which of these markers has the best test performance characteristics requires further study.[88]Like CRP, one of the most well-known and studied inflammatory markers shown to be associated with CVD, GlycA and GlycB are acute phase proteins with plasma concentrations that increase or decrease in response to changes in the levels of inflammation throughout the body.[89]CRP reflected the disease severity before treatment. CRP and SAA values were associated with helper T-cell proportions whereas ESR was associated with cytotoxic T-cell proportions, both being type 2 predominant.[90] Tuberculosis (TB) , including pulmonary disease, frequently presented without fever, sweats or weight loss and with normal blood inflammatory markers. This information is of as much relevance to policy makers seeking to improve active case detection as to clinicians and the general public.[91]Both CRP and SAA levels negatively correlated with the ratio of Th1/Th2. In contrast, ESR negatively correlated with the ratio of Tc1/Tc2.CRP reflected the disease severity before treatment and CRP and SAA values were associated with helper T-cell proportions whereas ESR was associated with cytotoxic T-cell proportions, both being type 2 predominant.[92]

Plasma levels of Lipo polysaccharide (LPS), Myeloid Differentiation (MD-2) and sCD14 can discriminate between activeTB and latent TB infection (LTBI). A decline in LPS and MD-2 concentrations were associated with response to anti-TB treatment. The clinical potential of these soluble TLR-4 pathway proteins needs to be further explored. The method for diagnosing TB is mycobacterial culture of pleural effusion (PE), pleura tissue, which requires weeks to yield. The treatment could thus be delayed, resulting in an increased mortality rate. In addition, mycobacterial culture is not so sensitive for PE and with positivity in less than two thirds of cases with TB pleurisy.[93]The MPV was lower in patients with pulmonary tuberculosis (PTB) than in healthy controls, however, the difference waslimited. The MPV does not reflect the severity of the disease. The use of MPV as an inflammation marker and a negative acute-phase reactant in PTB does not seem to be reliable.[94] Decreased plasma ghrelin levels, in addition to increased plasma inflammatory cytokine levels, may be associated with malnutrition in active pulmonary tuberculosis.[95]

Screening for and treatment of LTBI before infliximab therapy reduces the risk of developing active tuberculosis.New blood tests that measure INF-γ production are an alternative to traditional tuberculin skin testing and offer some significant advantages over skin testing for screening of LTBI.[96]IFN-γ response to antigens encoded by the region of difference 1 (RD1) of the *Mycobacterium tuberculosis*genome(ESAT-6, CFP-10, TB 7.7) and purified protein derivative (PPD) at different intervals afterART commencement and at time of TB-IRIS using assays of a whole blood IFN-γ release, IL-2 , IL-12, tuberculin skin test (TST) response at the same time points.[97]A previous study demonstrated unappreciate role for vitamin D supplementation in accelerating resolution of inflammatory responses during tuberculosis treatment. A potential role for adjunctive vitamin D supplementation has been suggested in the treatment of pulmonary infections to accelerate resolution of inflammatory responses associated with increased risk of mortality.[98]SICAM-1 is considered as one of the inflammatory mediators that undergoes fluctuations during TB disease; its level is very much related to the extent of lung involvement. Since the level of this marker declines after therapy, it could be used as a "Serum marker "in evaluating the therapeutic response observed during the follow- up.[99]

More research into the immunopathogenesis of TB-IRIS and diagnostic potential of cytokine markers is warranted.[100]Ghrelin but not leptin levels were significantly lower in the malnourished TB group than in the well-nourished TB group. Plasma levels of ghrelin tended to decrease as inflammatory cytokines increased before treatment.Decreased plasma ghrelin levels, in addition to increased plasma inflammatory cytokine levels, may be associated with malnutrition in active PTB [101]and increased circulating levels of free radical activity are also found and hence may play a role in the resultant fibrosis. It also reinforces the belief that a range of free radical activity (FRA) indicators are produced in any inflammatory process with fibrogenic potential and that these indicators may be measured at different stages of the disease process.[102]Albumin and hemoglobin levels and the albumin/globulin ratio in patients with PTB increased during the study period, regardless of the bacteriological results. High serum globulin levels

did not change among PTB patients during the study. Serum copper levels and the CRP/albumin ratio may be important parameters to evaluate the persistence of non-conversion after 60 days of TB treatment, and they may serve as predictors for relapse after successful treatment.[103]

Patients with complicated disease had significantly higher PLA2 levels on admission. PLA2 was not produced in a lipopolysaccharide-stimulated whole blood culture, indicating that PLA2 originates from other types of cells. These data indicate that PLA2 may be a mediator of disease in protracted inflammatory diseases such as thyroid fever.[104]Peripheral blood mononuclear cells produced significantly increased levels of a number of cytokines at the convalescent versus acute phase of infection, including IFN-γ, MIP-1β, sCD40L, TNF-β, IL-13, and IL-9. These results suggest that *S.* Typhi antigens induce a predominantly Th1 response, but that elevations in other cytokines may be modulatory.[105] The importance of ADA as a serum marker in addition to CRP for assessing the immune response in USA patients has been established.[106]Total sialic acid (TSA) and its lipid fraction and protein associated sialic acids shows that the levels of TSA and PASA were significantly higher in serum typhoid fever patients compared with normal controls and further studies are required to explore the binding of SA to the specific site of proteins and lipids to consider these inflammatory markers in monitoring and progression for typhoid fever disease, and evaluating the effectiveness of various therapeutic approaches.[107]The yellow fever virus (YEL) in hepatocyte injury results in prevalence of apoptosis over necrosis from a TGF-β action induced by the inflammatory response.[108]

Despite the disproportion between injury and inflammation, the cellular immune response plays an important role in the pathogenesis of the hepatocytic injury observed in YEL, probably as a result of cytolytic actions through mechanisms involving MHC II and the activation of Fas receptors and granzymes/perforins.[109]The differential cytokine production indicates that DENV2 results in TNF induction, which discriminates it from vaccine viruses that preferentially stimulate INF expression. These differential response profiles may influence the pathogenic infection outcome.[110]Patients with YEL associated neurotropic disease (YEL-AND) exhibited a cytokine profile similar to that found in vaccines without YEL vaccineassociated adverse events (YEL-AEs): elevated levels of RANTES and low levels of growth-related oncogene (GRO), monocyte chemotactic protein (MCP-1), transforming growth factor–β1, and TNF–β. That elevations in cytokine levels and reductions in platelet counts are suitable surrogate markers for patients likely to experience severe adverse reactions to YEL.[111]Vitamin A stores were positively associated with several measures of innate immune activity across a broad range of stores, suggesting that vitamin A enhances protection against diverse pathogens even at concentrations above those needed to maintain normal vision. The negative association of stores with serum IL-6 and IL-17 suggests that not all protective responses are similarly enhanced by vitamin A.[112]

CD4 knockout and Igh-6 mice were unable to resist challenge implicating that antibody in conjunction with $CD4^+$lymphocytes bearing a Th1 phenotype as the critical factors involved in virus clearance in this model.[113]Restricted virus replication and lysosomal compartmentalization may be important contributing factors to the success of the YF-VAX vaccine.[114]Additional prospective research incorporating serological markers of infectious agents or predictive markers of chronic inflammation should serve to elucidate the possible causal pathway of recurring or persistent infection in the etiology of prostate cancer in black men.[115]Sexually transmitted infections (STIs) may contribute to prostatic inflammation and cell damage in a subset of infected men. Further studies are warranted to replicate study findings and determine host and infection characteristics associated with large Prostate Specific Antigen increases.[116]The presence of vaginal neutrophils diagnosed by saline wet mount had a high sensitivity and negative predictive value, but shows a low specificity and positive predictive value for the diagnosis of upper genital tract infection.The presence of vaginal polymorphonuclear leukocytes has a high sensitivity and negative predictive value for the diagnosis of upper genital tract infection.[117]
The influence of estrogen in ICAM-1 expression suggests the beneficial effects of estrogen on the regulation of vaginal homeostasis. Identification and quantification of specific surrogate markers for the inflammatory response evoked by exogenous compounds and their regulation by estrogen will lead to an efficient strategy against sexually transmitted diseases including AIDS.[118]A nonclonal aspect of gamma-zone was constantly found and it

is possible that the differences are in accordance with the different evolutionary phases of the disease, and that the oligoclonal distribution is a marker of the autoimmune state of the disease.[119]Slow healers had deeper metabolic and coagulation defects at the start of antibiotic therapy. In addition to providing novel insight into Buruli ulcer pathogenesis showing a unique proteomic signature for this disease.[120]The identification of effective prognostic biomarkers could lead to earlier detection of high-risk patients, more patient-specific treatment options, and more productive clinical trials.[121]

Inflammatory, adhesion markers andwhole blood viscosity(WBV) may be associated with leg ulceration in sickle cell disease by way of inflammation - mediated vasoocclusion / vasoconstriction. Impaired skin oxygenation does not appear to be associated with chronic ulcers in patients with sickle cell disease.[122]Significantly increased levels of MCP-1, VEGF and EGF are observed in women exposed to prolonged psychosocial stress. Statistical analysis indicates that they independently associate with a significant risk for being classified as ill.MCP-1, EGF, and VEGF are potential markers for screening and early intervention in women under prolonged psychosocial stress.[123]A concentration of 316 parts per billion ZEA leads to a significant decrease in the levels of pro- and anti-inflammatory cytokines at both gene expression and protein levels, correlated.[124]The levels of expression of their respective chemokine receptors on T cell subsets may prove to be informative biomarkers for Lyme disease and related to specific disease manifestations.[125]Autism spectrum disorders associated with Lyme/tick-borne diseases may be mediated by a combination of inflammatory and molecular mimicry mechanisms. Greater interaction is needed between infectious disease specialists, immunologists and psychiatrists to benefit from this awareness and to further understand these mechanisms.[126]

CONCLUSION

A host of inflammatory markers identified in some of the major infectious diseases have been presented in this paper. While assays for some inflammatory markers such as IL-6, hsCRP, PCT, TNF-α, Immunoglobulins, CD4, CD8, ESR, TC, Gherlin and Leptin are available all of which could be used for diagnostic purposes, there are hundreds of other inflammatory markers which are identified and acceptable assays need to be developed. Many of the inflammatory markers identified in various infectious diseases are the outcome of many research carried out in this field. The contents of this review article will make awareness among researchers to establish reliable and cost saving assays for inflammatory markers to diagnose a host of infectious diseases.

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