

HAPTOGLOBIN: AN ACUTE PHASE RESPONSE PROTEIN WITH DIVERSE ROLES IN INFECTION AND SEPSIS

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Abstract - Haptoglobin(Hp) is a multifunctional plasma glycoprotein which plays a critical role in several physiological and pathological processes, particularly in the context of infection and sepsis. This review provides a comprehensive examination of diverse functions of Hp. It focuses on its role as positive acute phase response protein, its involvement in management of free hemoglobin, modulation of the immune response and its potential as a biomarker for a wide range of diseases. The review outlines Hp ability to bind and clear free hemoglobin which helps to prevent oxidative damage, while its immunoregulatory properties contribute to the body's defense against pathogens during infection and sepsis. Additionally, the article discusses the growing interest in Hp as a potential diagnostic and prognostic biomarker for various conditions, including infectious diseases, sepsis, and role of Hp in protein glycosylation. Recent studies have also emphasized the role of Hp in the stimulation of the inflammasome which is a key component of the innate immune response, further underscoring its multifaceted involvement in the body's defense mechanisms. By examining the current understanding of Hp multifaceted functions, we highlight the importance of further research into this versatile acute phase protein and its clinical implications.

INTRODUCTION

Microbes play a key role in maintaining human health and is also involved in causing varied infectious diseases and illness (Young, 2017). The infections caused by several microorganisms are the utmost challenge to the world and can exacerbate a multitude of responses within the human body (Hotchkiss *et al.*, 2016). The progression of bacterial infection starts with the initial establishment of bacteria within the host by adhesion, invasion and replication inside the host and cause impairment of host tissues (Hakansson *et al.*, 2018; Lazzaro *et al.*, 2022). The ultimate goal of the host defense system is to combat bacterial replication and eliminate bacterial invaders rapidly. This is accomplished by both the innate and adaptive immune responses (Keselowsky *et al.*, 2020; Hakansson *et al.*, 2018). The immune response activated by non-infectious agents is called systemic inflammatory response syndrome (SIRS) and infection-induced systemic immune response in the host is called sepsis (Castellheim *et al.*, 2009). The inflammatory responses in both SIRS

and sepsis are comparable and which may lead to multiple organ dysfunction syndrome (MODS) which eventually results in death of the host (Sygutowicz and Sitkiewicz, 2020; Cheng *et al.*, 2020). One of the most critical responses to infection is the acute phase response (APR), a quick and systemic reaction that involves various physiological changes aimed at combating pathogens and promoting healing (Fabrizio Ceciliani*, Alessia Giordano *et al.*, 2002; Mun *et al.*, 2024).

The acute phase reaction (APR) is triggered by elevated levels of cytokines from monocytes and various tissue macrophages in response to bacterial infections, damage of tissue, trauma, or post-surgical infections, plays a vital part in mitigating the development of sepsis (Das, 2021; Raju *et al.*, 2019). The immune system physiological response to sepsis can differ based on the patient, the causative organism, the infection site and sometimes even gender, making it challenging to develop effective diagnostic and treatment strategies (Raju *et al.*, 2019; Dias, Brouwer and Van De Beek, 2022). Early mortality due to sepsis is linked to severe

increase in pro-inflammatory cytokines or a delayed anti-inflammatory response (Marques *et al.*, 2023). Furthermore, the interactions among various leukocytes are crucial in coordinating the response to various septic stimuli, specifically for T-cell immunosuppression (Torres *et al.*, 2022). Cytokine network and its regulation of APR play a crucial role in this circumstance (Almalki *et al.*, 2022; Gierlikowska *et al.*, 2022).

The hepatic release of acute phase proteins (APPs) is initiated by elevated levels of TNF- α and IL-1 in response to infections, leading to production of second wave of cytokines that activate the release of stored APP from blood monocytes and neutrophils during APR (Heinrich, *et al.*, 1990; Raju *et al.*, 2019). Serum proteome profile analysis of sepsis patients has found numerous positive and negative APPs which are associated with progression of sepsis (Miao, Chen and Ding, 2021; Cao and Robinson, 2014). The elevated levels of serum Hp which is a positive acute phase protein correlate with reduced in-hospital mortality in sepsis patients admitted in ICU, while lower Hp levels are linked to an increased risk of mortality due to increased levels of free hemoglobin in the circulation (Kalenka *et al.*, 2006; Raju *et al.*, 2019). Elevated IL-6 levels in response to TNF- α and IL-1 β , is recognized as a major inducer of Hp expression (Chaudhry *et al.*, 2013; Peyssonnaud *et al.*, 2007). This review focuses on positive acute phase protein Hp and its multiple roles in infection, sepsis and innate immune response mechanisms such as those involving the inflammasome pathway.

Acute phase response and role in infection

The host's diverse reactions to various infections, inflammation, and trauma are collectively termed the acute phase response (APR). This response encompasses with broad spectrum of pathophysiological changes aimed at minimizing tissue damage and facilitating repair (Iskander *et al.*, 2013; Kerrigan *et al.*, 2019). Key features of the APR include fever (pyrexia), increased white blood cell count (leukocytosis), alterations in hormone levels and depletion of muscle proteins (Jain, Gautam, and Naseem 2011; Gyawali, Ramakrishna, and Dhamoon 2019). These physiological changes are essential for mobilizing the immune system and promoting healing during acute illness. A significant component of the APR is the liver's enhanced secretion of several serum proteins known as acute

phase proteins (APPs). This systemic response is complex, involving both local effects at the site of injury and broader systemic effects throughout the body (Grover *et al.*, 2016; Ehling, Wolf, and Bode, 2021). The APR is primarily initiated by cytokines, which act as signaling molecules among the local injury sites and the hepatocytes responsible for producing APPs. The cytokines produced by numerous immune cells have multiple sources and targets, influencing numerous biological functions. They play a significant role in orchestrating the immune response and have been identified in many animal species, including mammals, reptiles, birds, and even in starfish (Changes, 1999; Jain *et al.*, 2011).

The variations in APPs concentrations during the APR is mainly due to changes in their production by liver cells, for instance the production of C-reactive protein (CRP) and serum amyloid-A (SAA) can see increases of approximately 50% or more in response to inflammatory stimuli (Zhang *et al.*, 2019; Cray 2012). The interleukins IL-1, IL-2 and tumor necrosis factor- α (TNF- α), are particularly important in this process by stimulating hepatocyte cells to synthesize and secrete APPs. The peak concentrations of serum APPs generally reached within 24-48 hours following initial stimulus, the levels typically declining as the patient recovers from infection (DeLong and Born, 2004). Feedback regulatory mechanisms help to limit the APR, allowing it to resolve within 4 to 7 days if no further stimuli occur. However, repeated triggers can lead to a chronic state of APR, which may contribute to persistent inflammation and related health issues. The liver's response during the APR involves producing a range of positive APPs while simultaneously reducing the synthesis of certain proteins, classifying them as negative APPs (32). The negative APPs include proteins like transthyretin, transcortin, albumin, transferrin, and retinol binding proteins. These negative APPs are typically involved in maintaining homeostasis and regulating various physiological functions, but their levels decrease during the APR as the body prioritizes the synthesis of positive APPs.

Positive APPs serve various roles in the immune response. For example, CRP and Hp are known for their ability to directly combat pathogens. CRP promotes the opsonization of bacteria, enhancing their recognition and clearance by immune cells, Hp plays a significant role in sepsis (fig 1) as lower levels of serum Hp expression contributes to impaired acute phase response and increased Hp levels play

a protective role in sepsis. Hp binds free hemoglobin released during tissue damage, preventing oxidative stress and further cellular injury. Other positive APPs, such as fibrinogen and complement proteins are involved in coagulation and immune activation, contributing to the containment of infections (Prucha *et al.*, 2003; Sander *et al.*, 2010; Papp *et al.*, 2012).

The APR is also associated with metabolic changes, including anorexia and altered energy utilization. This shift helps redirect energy resources toward immune function and tissue repair, but prolonged APR can lead to muscle wasting and malnutrition, particularly in critically ill patients (Van Wyngene *et al.*, 2018). Understanding the APR mechanism is crucial for the development of

(ROS) (Naryzny and Legina, 2021). Beyond its hemoglobin-binding function, Hp plays diverse roles in physiological and pathological processes, including immune modulation, antioxidant defense, and acute phase response (Sultan *et al.*, 2013; Clerc *et al.*, 2016). Hp is composed of alpha (α) and beta (β) polypeptide chains connected by disulfide bonds. Primary structure of Hp includes a signal peptide followed by the α and β chains, with genetic variations leading to distinct phenotypes (Hp1-1, Hp2-1, Hp2-2). The α chain exhibits allelic variants (α 1 and α 2) due to gene duplication events, influencing Hp's structural and functional properties (Fig. 2A). In secondary and tertiary structures α and β chains fold into specific domains crucial for their interaction with hemoglobin and

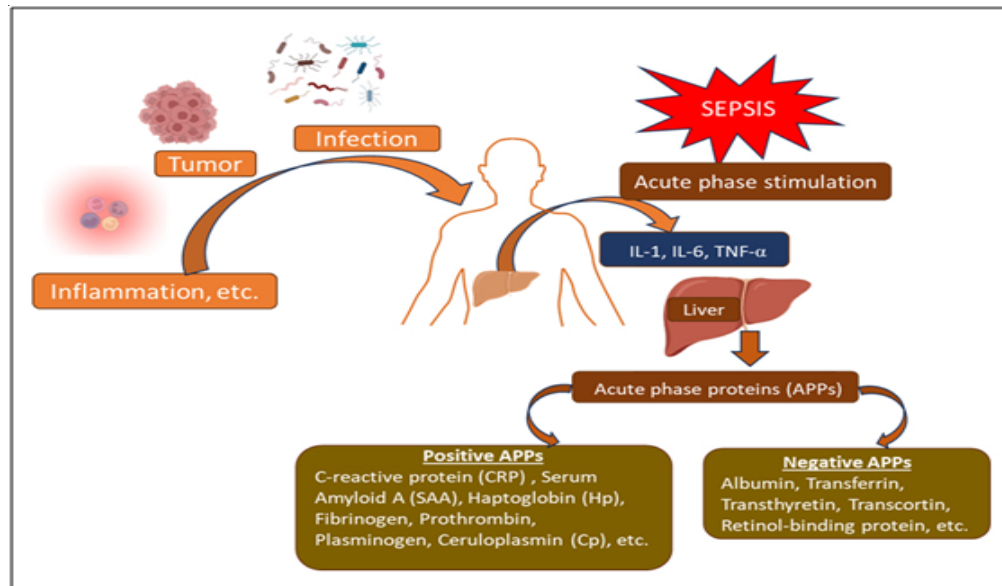


Figure 1. Production of acute phase response during infection and sepsis

therapeutic approaches to accomplish inflammatory diseases and improve patient outcomes (Alessandri *et al.*, 2013).

Structure and function of Haptoglobin

Hp is a conserved protein present in all the mammals, which was first identified in the year 1938 as component of blood plasma protein that binds to free hemoglobin. The name haptoglobin is derived from Greek word haptain, meaning to bind, combined with hemoglobin (Hb) thereby preventing oxidative damage and conserve iron release, hence reduce the generation of Reactive oxygen species

immune cells. Quaternary Structure Hp forms tetrameric ($\alpha_2\beta_2$) or polymeric structures (Hp2-2), influencing its binding affinity and biological functions in circulation (Golubeva 2023; Andersen *et al.*, 2017). Hp phenotypes are determined by variations in the α chain. Hp1-1 is homozygous for the α 1 allele, forming tetrameric structures. Hp2-1 heterozygous with one α 1 and one α 2 allele, forming mixed tetramers and polymers, Hp2-2 homozygous for α 2 allele, resulting in predominantly polymeric structures with altered functional properties. The concentrations of plasma Hp changes with pathology of disease, testing its concentrations is part of general clinical practice

(Naryzny and Legina, 2021).

Hp is primarily produced by hepatocytes and also can be synthesized in other tissues like the skin, lungs and kidneys (Naryzny and Legina, 2021; Andersen *et al.*, 2017). The reticuloendothelial system (RES) removes the Hp-hemoglobin (Hp-Hb) complex from the bloodstream. In cases of hemolytic anemia Hp levels typically decrease by binding to Hb. The Hp sequesters the iron portion contained in it, thereby preventing bacteria to utilize iron produced by the breakdown of red blood cells (RBC) (Chiabrando *et al.*, 2014). The laboratory testing of Hp is often conducted when a patient shows indications of anemia, fatigue and shortness of breath, along with physical signs of hemolysis like jaundice and dark urine (Robertson *et al.*, 2017).

A decrease in the Hp levels can support in diagnosis of hemolytic anemia, especially when seen together with a reduced RBC count, hemoglobin, and hematocrit value, as well as an elevated reticulocyte count. If the reticulocyte count rises while Hp levels remain normal, it may suggest that red blood cell damage is taking place in the liver or spleen, potentially indicating drug induced hemolysis or red blood cell dysplasia (Barcellini and Fattizzo, 2015). In such cases, the spleen and liver identify and eliminate defective RBC without releasing Hb into the bloodstream, which means Hp levels are normal in the blood stream. Therefore, if anemia symptoms are present, it is likely not due to hemolysis but rather some issue with cell production, such as aplastic anemia (Shih *et al.*,

2014). Decreased Hp levels without accompanying anemia symptoms may suggest liver dysfunction, as the liver may not be producing sufficient amounts (Smith and McCulloh 2015).

The primary role of Hp is to aid in clearance of freely circulating Hb in the blood stream. The Hb is the main blood plasma protein that mediates the detoxification of ROS and nitrogen species and also involved in movement of oxygen throughout the circulatory system (Nielsen *et al.*, 2010; Thomsen *et al.*, 2013; Quaye, 2008). As the physiologically aged RBCs destroyed at a rate of 2×10^6 cells per second, free hemoglobin is naturally released into the blood as a byproduct of intravascular hemolysis. When combined with additional comorbidities such as diabetes, viral diseases, trauma and malignancy, intravascular hemolysis can lead to a number of serious consequences (MacKellar and Vigerust, 2016). When Hp and Hb form a potent non-covalent complex (Hp-Hb), Hp is removed by the reticuloendothelial system and is endocytosed by CD163 protein present on hepatocytes, and macrophages (MacKellar and Vigerust, 2016; Pan *et al.*, 2020).

Hp which is a circulatory protein present in the range of 38 to 208 mg/dL in the blood, which is sufficient to bind and clear approximately 3g/dL of Hb effectively preventing free Hb from circulation in the body elucidated in (Fig. 2.B). The expression of CD163 protein on these cells is influenced by inflammation and cytokines like IL-1 and IL-6, with IL-6 playing a pivotal role in stimulating Hp production and modulating CD163 protein

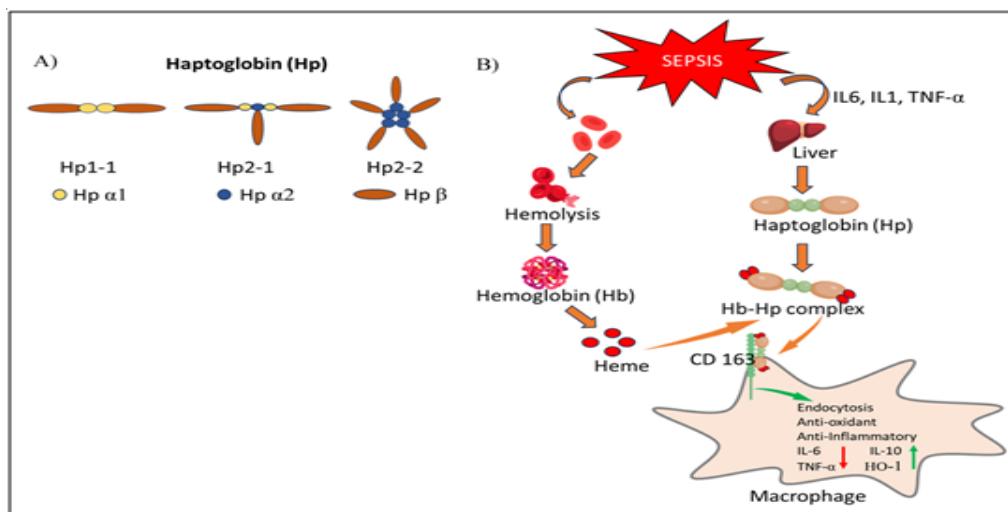


Figure 2. Structure of Haptoglobin and its role in sepsis: a) Haptoglobin forms; b) Pathway depicting clearance of hemoglobin by Haptoglobin in sepsis

expression on the host cell surface (Huntoon *et al.*, 2008). In contrast the expression CD163 is down regulated by TNF- α , IL-4 and interferon- γ . This regulatory progression is carefully regulated by the release of various immune modulatory molecules (Thomsen *et al.*, 2013).

When Hb binds to Hp for its clearance, the Hp-Hb complex is internalized, processed and degraded, releasing heme. The heme is then further broken down by heme oxygenase-1, releasing iron that can be recycled for the synthesis of new Hb proteins (Andersen *et al.*, 2017; Smith and McCulloh, 2015). Unbound Hp is removed from the plasma within the span of 72-96 hours, whereas the Hp-Hb complex is removed much faster, with a clearance time of approximately 20 minutes. Unlike iron the Hp is not recycled during this process as Hp is degraded and newly synthesized to replenish blood and tissue levels (MacKellar and Vigerust 2016; Frimat, *et al.*, 2019). Due to lack of an efficient clearance system, the free Hb can catalyze the generation of free radicals, which leads to demolition of cellular components and extracellular macromolecules. It can also stimulate the oxidation of LDL cholesterol, contributing to potential tissue damage (Quaye, 2015; Jomova *et al.*, 2023).

Antioxidant Activity

Hp binds to freely circulating Hb with high affinity, mitigating its harmful effects of iron in the circulation (Buehler *et al.*, 2020). Excess iron can cause increased risk of sepsis and mortality during infections and atherosclerosis by generating ROS by the processes like Haber-Weiss reaction, producing damaging hydroxyl radicals. These radicals drive lipid peroxidation, amplifying tissue damage through iron-dependent mechanisms (Bozza and Jeney, 2020; Gutteridge, 1987). The progression of sepsis involves various molecular mechanisms, particularly the dysregulation between reactive oxygen species (ROS) generation and their elimination through cellular antioxidant pathways (Abelli *et al.*, 2022). Excessive production of oxygen free radicals in sepsis contributes significantly to multiple organ failure and increased mortality. Studies on sepsis have consistently highlighted oxidative imbalance and elevated oxidative stress (OS), driven by factors such as hypotension, microvascular thrombosis, mitochondrial injury from OS and inflammation (Sahoo *et al.*, 2024; Mantzaris *et al.*, 2017). Survivors of sepsis showed

greater antioxidant potential compared to non-survivors, with antioxidant levels rising rapidly to normal or supranormal levels in survivors (Rocha *et al.*, 2012). Hp's antioxidant efficacy varies by genotype. Research by Melamed-Frank *et al.*, (2001) indicates that Hp1-1 genotype offers superior protection against oxidative damage due to better access to extravascular space, while Hp2-1 and Hp2-2 genotypes result in prolonged free Hb circulation, increasing oxidative stress. Hp2-2 genotype is linked to reduced antioxidant capacity and heightened susceptibility to oxidative damage (Melamed-Frank *et al.*, 2001).

Immunoregulatory Role of Hp

Hp as an APP, not only exhibits significant antioxidant properties also can play a vital immunoregulatory role in sepsis. Hp is involved in modulating immune responses, as observed with studies dating back to 1968, including those reported by Langlois and Delanghe, demonstrating enhanced immune activity in individuals with the Hp2-2 genotype, such as greater antibody production following vaccination. Additionally, Hp inhibits prostaglandin synthesis, contributing to its anti-inflammatory effects (Blackburn *et al.*, 2018).

Hp is instrumental in regulating the equilibrium between T helper 1 (Th1) and T helper 2 (Th2) responses. For instance, the Hp1 phenotype, when complexed with hemoglobin, promotes a robust Th1 response, which enhances defenses against intracellular pathogens while suppressing Th2 cytokine release. This Th1-skewed response provides a protective advantage against infections (Guetta *et al.*, 2007; Martynova *et al.*, 2022). Furthermore, polymorphisms in the Hp gene are linked to immune-mediated conditions, including Crohn's disease, rheumatoid arthritis and celiac disease, highlighting its broader immunological significance.

In sepsis elevated plasma Hp levels plays a protective role in aiding the host response to infections. The elevated levels are associated with improved outcomes as Hp helps modulate inflammation and immune responses, thereby reducing organ damage and mortality risk in sepsis (Janz *et al.*, 2013; Smith and McCulloh, 2015).

Role of Hp in Angiogenesis and Wound Healing

Hp plays a multifaceted role in sepsis, extending beyond its antioxidant and immunoregulatory

functions to influence angiogenesis and wound healing, which are critical for tissue repair (Thornton *et al.*, 2015; Andrés *et al.*, 2022). Hp is shown to up regulate vascular endothelial growth factor (VEGF) and their receptors particularly in its pro-haptoglobin form, promoting endothelial cell sprouting and branching. This angiogenic activity facilitates wound healing by enhancing neovascularization and tissue regeneration (di Masi *et al.*, 2020). In sepsis, where tissue damage and vascular dysfunction are prominent, Hp supports the restoration of vascular integrity and repair of injured tissues by stimulating angiogenesis. These properties not only aid in mitigating organ damage but also contribute to overall recovery by improving blood flow to damaged areas, reducing ischemia and promoting regeneration (Thornton *et al.*, 2015; Moreno *et al.*, 2009). Hp plays a protective role in angiogenesis and tissue repair mitigating organ damage and aiding recovery. Angiogenic effects of Hp must be carefully regulated to avoid contributing to pathological processes, particularly in patients with cardiovascular disease and sepsis. These diverse roles underline Hp importance in balancing tissue repair and immune responses during sepsis (Smith and McCulloh, 2015).

Role of Haptoglobin on Nitric Oxide (NO) levels

Nitric oxide (NO), a key mediator of vascular homeostasis, is higher quantities during sepsis, due to the activation of inducible nitric oxide synthase (iNOS). While NO at moderate levels are essential for vascular relaxation and immune defense, its overproduction can lead to pathological vasodilation, hypotension, vascular leakage, and oxidative stress, all of which exacerbate septic shock and organ dysfunction (Osuru *et al.*, 2023; Wobeto *et al.*, 2008). Hp plays a significant role in moderating the detrimental effects of excessive nitric oxide (NO) production during sepsis. It contributes to NO regulation primarily through its ability to bind and neutralize cell-free hemoglobin (Hb). Free Hb, released during hemolysis, reacts with NO to form highly reactive and damaging molecules like peroxynitrite (Gwozdziński *et al.*, 2021). By sequestering cell-free Hb, Hp prevents this reaction, preserving NO bioavailability and reducing oxidative damage to vascular and tissue structures (Su *et al.*, 2020).

Moreover, Hp indirectly influences NO levels by attenuating inflammatory responses and oxidative stress, which drive excessive NO production. By

modulating NO levels, Hp supports vascular stability, prevents severe hypotension and reduces the risk of vascular injury, all critical in managing sepsis and improving patient outcomes (Rodrigues *et al.*, 2019).

This regulatory effect on NO, combined with Hp's antioxidant, immunoregulatory, angiogenic, and wound-healing properties, underscores its multifaceted protective role in the pathophysiology of sepsis (Roth-Walter *et al.*, 2024).

Plasma levels of Haptoglobin and Diagnostic Potential

Plasma Hp levels vary with clinical conditions, rising in response to trauma, burns, inflammation and cancer due to its acute phase role in removal of oxidative species (Thornton *et al.*, 2015). Elevated Hp levels peak for few days upon inflammatory or traumatic events subsequently normalize within weeks. Conversely, low Hp levels are associated with malnutrition, hemolysis, hepatic diseases, allergies and seizures (Cray, 2012). Hp genotype significantly influences disease outcomes, with the Hp 2-2 genotype found in approximately 36% of the population. Studies involving nearly 175,000 patients highlight its association with higher cardiovascular risk (Dalan *et al.*, 2016). Rapid genotype identification could guide targeted therapies, such as vitamin E or C supplementation, reducing cardiovascular disease (CVD) progression by 30–40%. For instance, 400 IU of vitamin E can neutralize oxidative stress, stabilize LDL particles and mitigate atherosclerotic plaque growth (Ziegler *et al.*, 2020).

Role of Hp in infection and Sepsis

Sepsis is a critical medical condition that occurs when the body's response to an infection causes harm to its own tissues and organs (Nedeva, 2021; Jarczák *et al.*, 2021; Huang *et al.*, 2019). It leads to severe inflammation, tissue damage and multiple organ failure, often necessitating urgent medical intervention (Mas-Celis *et al.*, 2021; Salomão *et al.*, 2019). Despite of advancements in medical facilities, it remains as major global health issue because of its high death rate and difficulty in management (Schlapbach *et al.*, 2020). Sepsis is divided into three main groups based upon its severity. **Sepsis** is the initial stage where the body responds to an infection with a systemic inflammatory response (Thompson *et al.*, 2013; Delano and Ward 2016). The Symptoms

Table 1. Criteria used for diagnosis of sepsis

S.No	Variable	Signs and Symptoms
1	Basic parameters	Fever >98 F° or < 98F° Heart rate >90 bpm Tachypnea Changes in mental status Edema
2	Hemodynamic examinations	Hypotension 90/60 mm Hg Hyperglycemia
3	Inflammatory responses	WBC count >12000 or <4000 Platelet count <100,000 Elevated C-reactive protein in serum >10 Elevated Procalcitonin in serum
4	Organ dysfunction abnormalities	Hypoxemia Hyper oliguria Elevated creatinine levels Clotting abnormalities Activated partial thromboplastin time Elevated Bilirubin levels

Table 2. Quick sequential organ failure assessment (qSOFA) score

S.No	Assessment	Values
1	Lower blood pressure	≤ 100 mmHg
2	Higher respiratory rate	≥ 20 breaths per minute
3	Changed mental condition	GCS ≤14

of sepsis include fever, increased heart rate, breathing rate, and confusion. **Severe sepsis** is characterized by the presence of sepsis along with signs of organ dysfunction or failure. The most severe form of sepsis is **septic shock** and involves a significant drop in blood pressure that doesn't respond adequately to fluid replacement (Hotchkiss, 2017), this can lead to multiple organ failure and requires immediate medical treatment in ICU. The criteria used to diagnose sepsis are mentioned in the (Table 1) and Quick sequential organ failure assessment (qSOFA) score which is followed to assess the risk of patients with sepsis mentioned in the (Table 2) (Sohn *et al.*, 2019). Sepsis is typically triggered by an infection that can be caused by any microorganism. The common cause of infection leading to sepsis includes lungs conditions such as pneumonia, which can lead to sepsis (Lin *et al.*, 2018). Abdominal infections like appendicitis, peritonitis, gallbladder infections and urinary tract infections, particularly in the elderly, can cause sepsis. Skin infections, such as cellulitis, or

infections associated with wounds or surgical sites and other sources of infections in the bloodstream, heart (endocarditis), or central nervous system (meningitis) may also lead to sepsis (Lopez *et al.*, 2011; Sartelli *et al.*, 2024).

Previous studies have reported increased plasma Hp levels in both children and adults with sepsis have been incorporated into diagnostic algorithms for sepsis, serving as a marker of illness (Bhandari 2014; Leonard *et al.*, 2024). Elevated Hp levels in sepsis are linked to a protective role, improving outcomes regardless of illness severity or cell-free hemoglobin levels. The serum Hp levels are related with lower in hospital mortality in sepsis patients admitted in ICU, while reduced Hp levels correlate with higher mortality risk due to increased circulating free hemoglobin (Janz *et al.*, 2013; Raju *et al.*, 2019). IL-6 induced by TNF α and IL 1 β is recognized as the primary regulator of Hp expression (Narazaki and Kishimoto, 2018).

Role of Hp in inflammasome activation

Inflammasomes are a group of protein complexes that play a significant role in the innate immune system response to pathogens and cellular damage (Yao *et al.*, 2024). They activate caspase-1 which helps in the maturation and release of pro-inflammatory cytokines like IL 1 β and IL 18. These cytokines activated by caspase-1 contributes to inflammation, but excessive activation can be

detrimental, leading to tissue damage (Chen *et al.*, 2023). Current studies have highlighted the role of Hp in regulation of inflammasome as a key component of the innate immune system (Castellheim *et al.*, 2009). The inflammasome complex plays a significant role in the activation of inflammatory pathways, leads to the production of pro inflammatory cytokines, such as interleukin 1 α and interleukin 1 (Zheng *et al.*, 2020; Blevins *et al.*, 2022). Hp can inhibit the activation of the inflammasome, thereby dampening the inflammatory response and potentially contributing to the resolution of inflammation (Bailey *et al.*, 2013). By modulating the inflammasome, Hp can exert a protective effect against the excessive and uncontrolled inflammation that is often associated with infectious diseases and sepsis (Kumar 2018; Yang *et al.*, 2022). The ability of Hp to regulate the inflammasome activation is predominantly relevant in sepsis, in which altered immune response and the development of a pro-coagulant state is a key pathophysiological state (Wynn and Wong, 2017; Miao *et al.*, 2021). Hp's role in inflammasome activation is complex and not fully understood. Some studies suggest that Hp might be able to suppress inflammasome activation. For instance, research has shown that Hp can reduce the production of IL-1 β , a key pro-inflammatory cytokine released upon inflammasome activation (Salgar *et al.*, 2023). However, the exact mechanisms by which Hp might inhibit inflammasome activation are not yet fully elucidated.

CONCLUSION

Hp is an acute phase protein produced by the liver helps to scavenge freely circulating Hb. It plays a crucial role in regulating antioxidant and immune regulatory activities in infections including sepsis. It also regulates angiogenesis, nitric oxide reduction and wound healing. Increased Hp levels are indicator of several infections including sepsis and hence, the elevated levels of Hp can be used as a diagnostic marker. Finally, the diverse roles of Hp as a positive acute phase protein and rendering it as a crucial plasma protein which plays significant role in innate immune response in and infections and inflammasome activation.

Author Contributions

RK, AP, SK, SB: Conceptualization, organization, contributions at all stages, and drafting the majority

of the manuscript. RK, AP And KM: manuscript preparation and editing. SB and SK: editing and reviewing manuscript, supervision and funding.

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