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Acute phase proteins patterns as biomarkers in bacterial infection: Recent insights

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Abstract
Escherichia coli is a bacterium with command and pathogenic variants. It has been implicated in the induction of several inflammatory conditions. Finding a biomarker for infection began many years ago. The challenge of using acute phase proteins (APPs) as biomarkers for infection is a promising target for many researchers in this field. Many APPs have been studied for their roles as biomarkers of *E. coli* infection. The following review aims to highlight recent trials that have approved the use of adiponectin, amyloid A, ceruloplasmin, C-reactive protein, Haptoglobin, and Pentraxin 3 as biomarkers for *E. coli* infection and assess the obtained results. In conclusion, despite the existing approaches for the use of APPs as biomarkers in *E. coli* infection, we recommend more precise studies to enable these markers to be more specific and applicable in clinical fields. APPs could be markers for systemic inflammatory conditions, regardless of the causative agent.
Keywords: Adiponectin, Ceruloplasmin, C-reactive protein, *Escherichia coli*, Haptoglobin.

Introduction

Escherichia coli is considered a paradigm for various bacterial species that have both commensal and pathogenic variants (Leimbach *et al*., 2013). It is classified as a rod-shaped, gram-negative bacterium belonging to the Enterobacteriaceae family. Although it can invade any organ, bacteria usually inhabit the guts of humans and other warm-blooded animals (Rumball *et al*., 2023). Distinguishing these species is difficult because of their instability, criteria, and character shifting (Cobo-Simon *et al*., 2023). The pathogenicity of *E. coli* depends on phenotypic traits and the expression of specific virulence factors (Sheikh and Fleckenstein, 2023). *Escherichia coli* is associated with many inflammatory conditions and diseases such as cholangitis (Zhang *et al*., 2022), Urinary tract infection (UTI) (Hashimoto *et al*., 2022), traveller's diarrhoea (Muzembo *et al*., 2022; Yates, 2005), neonatal meningitis (Ku *et al*., 2015; Barichello *et al*., 2023), and pneumonia (Coe *et al*., 2022). This gives *E. coli* important value in the field of clinical research. Acute phase proteins (APPs) (Table 1) are early reactants in the majority of infectious diseases. They are involved in the acute phase response as part of innate immunity. APP patterns are altered in *E. coli* infection in many conditions and can be used to differentiate diarrhea caused by *E. coli* from other pathogens (Balikci and Al, 2014). The question here is whether this pattern change of APPs in serum and tissues of experimental models developed to be a potent marker for the diagnosis of *E. coli* infection. In addition, this pattern change could be used for early detection of infection. We focused on the recent involvement of APPs in *E. coli* infection and evaluated their role as diagnostic biomarkers or predictive parameters for *E. coli* infection.

Are acute phase proteins considered biomarkers for E. coli infection?

What is the biomarker?

Table 2 shows APP patterns that have been studied for their use as biomarkers of *E. coli* infections. The definition and criteria of biomarkers were considered. Biomarkers are defined as biological substances that can be measured and provide an indication of physiological and pathological conditions or responses to exposures and interventions. As shown in Figure 1, Biomarkers should be specific for diagnosis and useful in monitoring, prediction, and prognosis of the disease (Kunc *et al*., 2020).

Why are we seeking biochemical markers for bacterial infection?

From our point of view, the biomarker used for detecting a bacterial infection should facilitate rapid

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Table 1. Common APPs and their activities in the body.

Acute phase proteins	Activity	References
Adiponectin	- Anti-diabetic - Anti-inflammatory and antiapoptotic - Anti-obesogenic - Antiatherogenic - Cardio- and neuroprotective - Energy and metabolic hemostasis	(Meacham *et al*., 2022; Shklyaev *et al*., 2021).
Ceruloplasmin	- Antioxidant activity - Multicopper oxidase	(Liu *et al*., 2022)
C-reactive protein	- Facilitates phagocytosis - Removes necrotic debris.	(Kushner, 2023)
Haptoglobin	- Angiogenesis and lymphangiogenesis activities. - Antibacterial activity. - Antioxidant activity - Eliminates free hemoglobin - Immunomodulatory activity - Inactivates Nitric Oxide	(MacKellar and Vigerust, 2016)
Pentraxin 3	- Inhibits Complement-driven Macrophage Activation. - Modulates macrophage reprogramming. - Regulates innate immune response, inflammation, vascular integrity, tissue repair, and the complement system.	(Goncales *et al*., 2022; Yin *et al*., 2022)
Serum amyloid A	- Anti-inflammatory activity - Chemotaxis (cytokines-like activities)	(Sack, 2020)

Table 2. List of common APP patterns associated with *E. coli* infection.

Acute phase proteins	Pattern	References
Adiponectin	Decreased	(Tvarijonaviciute *et al*., 2011)
Ceruloplasmin	Increased	(Hyre *et al*., 2017)
C-reactive protein	Increased	(Hasan *et al*., 2022)
Haptoglobin	Increased	(Sadat *et al*., 2023)
Pentraxin 3	Increased	(Buerfent *et al*., 2019)
Serum amyloid A	Increased	(Kromann *et al*., 2022)

diagnosis, predict infection patterns and prognosis, correlate with the consequences of the infection, and be used to monitor therapy and eradication. However, the question here is whether there is a biomarker specific to a unique bacterial infection. If there is, this will save time for multiple and complicated microbiological investigations of such bacteria, and it will save our time consumed in culturing. Currently, CRP and PCT levels can be routinely measured in clinics as biomarkers of bacterial infections. Others have directed the use of different markers to differentiate between bacterial and viral infections (He *et al*., 2022), despite there being no single biomarker for such differentiation to date. Biomarkers can also be used to differentiate between infectious and non-infectious inflammatory conditions (Zandstra *et al*., 2021). Here, we focused on the use of different APPs as markers for *E. Coli* infection.

Acute phase proteins that are used as biomarkers for E. coli infection

Adiponectin

Table 1 shows the activities of adiponectin as a member of AAPs. It has been shown that mice with knockout

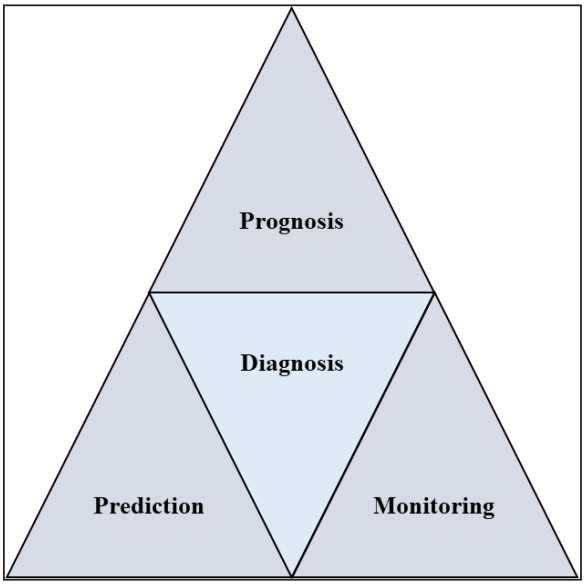

Fig. 1. Triangle shows that biomarkers can be specific for diagnosis and useful in monitoring, prediction, and prognosis of the disease.

adiponectin showed a more severe inflammatory response and kidney damage than wild-type mice after *E. coli* infection; however, after administration of exogenous adiponectin, the inflammatory response was alleviated. Adiponectin is negatively correlated with CRP and haptoglobin (HP) during acute endotoxemia induced by *E. coli* (Tvarijonaviciute *et al*., 2011). Alterations in adiponectin levels are strongly correlated with the existence of normal flora in the intestines, which affects the normal health of the intestines in rats (Peng *et al*., 2020). Low levels of adiponectin are also correlated with higher *E. coli* content in the intestines of patients with prostate cancer and metabolic syndrome. Although adiponectin is related to *E. coli* infection and propagation, it could not be considered a specific marker for *E. coli* infection. Tables 3 and 4 demonstrate other involvements and associations in many microbial and non-infectious conditions.

Ceruloplasmin

CP is a copper transport protein that is involved in the regulation of copper and iron metabolism (Table 1). In addition, it has ferroxidase activity and is induced during inflammatory conditions due to infection (Liu

Table 3. APPs associated with microbial infections.

Acute phase proteins	Microbial infections	References
Adiponectin	- Adenovirus - Aspergillosis - *Brucella abortus* - COVID-19 - Filariasis - *Helicobacter pylori* - *Heligmosomoides polygyrus* - Hepatitis B - Hepatitis C - Influenza - *Mycobacterium tuberculosis* - *Puumala hantavirus* - *Strongyloides stercoralis* - *Trypanosoma cruzi*	(Pesce Viglietti *et al*., 2020; Santamaria *et al*., 2021; Sibi *et al*., 2022; Queiroz-Glauss *et al*., 2022,)
Ceruloplasmin	- COVID-19 - Cytomegalovirus - Hepatitis B - HIV - *Staphylococcus aureus*	(Kang *et al*., 2020)

(Continued)

Acute phase proteins	Microbial infections	References
CRP	- *Aeromonas hydrophila* - *Brucella melitensis* - COVID-19 - Hepatitis B and C - Herpes virus - *Klebsiella pneumoniae* - *Paracoccidioides brasiliensis* - *Proteus mirabilis*	(Beimdiek *et al*., 2022; Yadav *et al*., 2021).
Haptoglobin	- *Mannheimia haemolytica* - *S. aureus* - *Trueperella pyogenes* - COVID-19	(Bassel *et al*., 2022; Beimdiek *et al*., 2022; Husnain *et al*., 2023).
Pentraxin 3	- *Aspergillus fumigatus* - COVID-19 - Dengue virus - Hepatitis B, C - HIV infection - *Klebsiella pneumoniae* - *Pseudomonas aeruginosa* - *Shigella* infection - *Staphylococcus aureus* - *Streptococcus suis* - *Trichinella spiralis*	(Asgari *et al*., 2021; Genc *et al*., 2021).
Serum amyloid A	- *Mycoplasma pneumoniae* - *Staphylococcus aureus* - Hepatitis C virus - COVID-19	

et al., 2022). Recently, CP has been used as a biomarker to evaluate *E. coli* and *Staphylococcus aureus* infections (Sadat *et al*., 2023). CP levels have also been used to evaluate the bioactivity of silver nanoparticles against *E. coli* infection (Skomorokhova *et al*., 2020). CP was used to evaluate the effect of *E. coli* LPS challenge in animals. High levels of CP in the serum of *E. coli* (LPS)-inoculated animals were reduced by anti-inflammatory agents in a drug- and dose-dependent manner (Manzari Tavakoli *et al*., 2020). Although there was a relationship between the CP serum pattern and *E. coli* infection, it was not a unique marker for *E. coli* infection. Table 3 shows the involvement of CP in other bacterial and microbial infections. Accordingly, from the previously mentioned in Tables 3 and 4, CP is associated with *E. coli* and other microbial infections, as well as non-infectious inflammatory conditions. CP could not be considered a specific marker for *E. coli* infection but could be a marker for systemic inflammatory response.

C-reactive protein

The precise CRP activity levels are shown in Table 1. Clinically, CRP is widely used to assess inflammatory response, although some records have stated its unclear function (Cheng *et al*., 2022). Records have confirmed their role in the potentiation of phagocytosis (Kinoshita *et al*., 2021). Its serum level is widely used as a marker for infection/inflammation in emergency circumstances, point-of-care tests, and for the differentiation of viral and bacterial infections (Levinson and Wasserman, 2022). The serum level of CRP has been approved as a diagnostic marker for patients with sepsis and determines the level of *E. Coli* infection in patients

Table 4. APPs associated with non-infectious conditions.

Acute phase proteins	Conditions	References
Adiponectin	- Alzheimer-like pathologies. - Atherosclerosis - Multiple sclerosis - Myocardial fibrosis - Hidradenitis suppurativa - Chronic bronchitis	(Khudiakova *et al*., 2022; Nyirenda *et al*., 2021).
Ceruloplasmin	- Dysregulation of lipid metabolism - Rheumatoid arthritis - Non-Alcoholic steatohepatitis - Wilson's disease - Rheumatoid arthritis	(Raia *et al*., 2023; Voros *et al*., 2023).
CRP	- Immunomodulation - Alzheimer's disease - Atherosclerotic cardiovascular disease - Immunothrombosis and venous thromboembolism. - Vitamin D deficiency - Bipolar disorder - Hypertension - Prediabetes and diabetes mellitus - Autoinflammatory diseases - Obesity - Systemic lupus erythematosus - Cancers - Depression	(Chae *et al*., 2022; Suzuki *et al*., 2022; Thomas-Dupont *et al*., 2022; Zhou and Hypponen, 2023,).
Haptoglobin	- Immunomodulation - Microangiopathic hemolytic anemia - Type 2 diabetes mellitus - Periodic fever syndrome - Sarcopaenia - Fulminant necrotizing enterocolitis	(Jaffey *et al*., 2022; Karim *et al*., 2022; Nakamura *et al*., 2023).
Pentraxin 3	- Hemorrhagic fever - Acute coronary syndrome - Rheumatoid arthritis - Kawasaki's disease - B-cell lymphoma, - Giant cell arteritis - Secondary hemophagocytic lymphohistiocytosis. - Acute migraine attack - Vasculitis - Myasthenia gravis	(Sammel *et al*., 2021; Vural and Albayrak, 2022; Jonasdottir *et al*., 2023).

(Continued)

Acute phase proteins	Conditions	References
Serum amyloid A	- Polycystic ovary syndrome - Kidney disease - Acne vulgaris - Parkinson's disease - Autoinflammatory diseases - Atherosclerosis - Ischemic stroke - Acute pancreatitis - Amyloidosis - Eosinophilic granulomatosis with polyangiitis. - Appendicitis - Clear cell renal cell carcinoma - Liver disease - Lung adenocarcinoma - Inflammatory rheumatic diseases	(Soric Hosman *et al*., 2020; Shi *et al*., 2022; Karam *et al*., 2023; Tong *et al*., 2023; ,).

with sepsis (Li *et al*., 2022). Mouse models have been used to elucidate the immune function of CRP in many trials to isolate and characterize endogenous CRP (Cheng *et al*., 2022). It has been used to differentiate between upper and lower UTIs induced by *E. Coli*; CRP levels were higher in upper than in lower UTIs, which enables determination of the anatomical position of UTIs and the method of therapy (Narayan Swamy *et al*., 2022). It was elevated in the sera of women with recurrent reproductive *E. coli* (Hasan *et al*., 2022). CRP is used as a biomarker for the prediction of bacteremia in children with febrile neutropenia, and it has been used with procalcitonin to predict bacterial infection in acute leukemic children (Nahar *et al*., 2023). It has also been used as a marker for the detection of neonatal sepsis induced by *E. coli* (Balayan *et al*., 2020). It can also be used to distinguish bloodstream infections from negative ones (Tang *et al*., 2020). In combination with WBC count, CRP level could be used as an improved diagnostic tool for gynecological and obstetric patients with infection (Jin *et al*., 2022). Although huge data have confirmed the association of high serum levels of CRP with *E. coli* infections, other data have also confirmed its association with other bacteria such as *Streptococcus pyogenes* (Germont *et al*., 2020), *Proteus mirabilis, Staphylococcus lentus, and Citrobacter braakii* (Lenicky *et al*., 2021). Regardless of the causative bacteria, CRP levels were increased in the sera of infected models, the matter which opened the debate for the ability to consider whether CRP is a specific marker for one species of bacteria or not. As previously mentioned, CRP can be considered a biomarker for the condition induced by the bacteria, not by the bacteria itself.

Haptoglobin

As shown in Table 1, HP is an APPs with antibacterial activity. Recent assays have been developed to detect only minute amounts of HP as a biomarker for *E. coli* infection (Nirala *et al*., 2020). A positive correlation between the number of *E. coli* colonies and HP serum levels was observed in animals infected with *E. coli* (Martin *et al*., 2021). HP has been approved for use in the differentiation between healthy and *E. coli*-infected animals; it started to be elevated in the sera of infected animals 4 days post-infection (Kromann *et al*., 2022). Similarly, *E. coli* enhances the serum levels of HP in infected animals (Wong *et al*., 2022, Husnain *et al*., 2023). In a transcriptomic study for the detection of differentially expressed genes between control and *E. coli*-infected animals, HP was upregulated in the infected groups. In contrast, administration of lipopolysaccharides derived from *E. coli* did not affect the level of HP in the serum of animals (Samarasinghe *et al*., 2020). Similarly, HP serum levels were not affected by fulminant necrotizing enterocolitis associated with *E. coli* infection in preterm infants (Nakamura *et al*., 2023). Moreover, mice affected by hemolytic uremic syndrome and deficient in HP showed low survival rates, and administration of a low dose of HP was associated with amelioration of kidney pathology (Pirschel *et al*., 2022). Serum HP was elevated 24 hours after administration of bacterial lysate formed from *S. aureus* and *E. coli* in the examined animals (Bassel *et al*., 2020). Recent clinical studies have revealed that HP was increased in the

serum of animals suffering from mastitis induced by *E. coli* and *S. aureus* (Sadat *et al*., 2023). In contrast, HP levels declined in the serum of animals infected with the probiotic *Bacillus subtilis* strain as a result of the ameliorative effect of probiotics on the immune status of animals (He *et al*., 2020). The serum levels of HP were associated with other microbial infections and many inflammatory conditions, as shown in Tables 3 and 4. This matter dismisses its use as a specific marker for *E. coli* infections. Furthermore, the detection of HP phenotypes and using specific-phenotypic determinates are very important for linking HP levels to infection/inflammation conditions, and the concept of one fit for all is not recommended here (Skytthe *et al*., 2022).

Pentraxin 3 (PTX3)

Table 1 shows the activity of PTX3. Its antimicrobial power enables it to play a pivotal role in the defense against uropathogens (Miao and Abraham, 2014). Biochemically, it is a carbohydrate-binding protein of two domains, the N-terminal domain and the C-terminal domain, which is similar to CRP (Daigo and Hamakubo, 2020). The properties of PTX3 are similar to antibodies (Garlanda *et al*., 2016). Its high levels in the plasma of patients with bacteremia in the first days of infection encouraged its use as a potent prognostic marker (Huttunen *et al*., 2011). Regarding its use as a marker for *E. coli* infection, it has been detected that PTX3 secretion in the urine of humans and mice is markedly increased during UTIs (Burkhardt *et al*., 2019). In contrast, mice deficient in PTX3 lost their capacity to clear *E. coli* from their urinary tract. The authors reported that PTX3 secretion in urine was markedly enhanced in humans and mice following UTIs and that mice deficient in PTX3 were highly impaired in their capacity to clear uropathogenic *E. coli* following vesicular challenge (Jaillon *et al*., 2014). Moreover, high serum levels were associated with the prediction and diagnosis of COVID-19, hepatitis B, hepatitis C, and other microbial infections, as shown in Table 3. Accordingly, PTX3 could be considered a biomarker for predicting and diagnosing systemic inflammatory conditions (Table 4), regardless of the type of causative agent, whether *E. coli* or other microbial or non-microbial agents.

Serum amyloid A (SAA)

Table 1 shows the main activities of as APPs. It acts on many types of leukocytes in response to inflammation, infection, and/or injuries (Abouelasrar Salama *et al*., 2020). Clinically, it has been used as a potent marker of chronic inflammation (Zhang *et al*., 2019). Regarding its usage as a marker for *E. coli* infection, at the molecular level, its expression was increased in the conditions of *E. coli* infections (Murata *et al*., 2020) and its serum level could be used as a clinically sensitive biomarker for multiple inflammatory conditions induced by *E. coli* infections such as UTIs (Erman *et al*., 2012), septic arthritis at which its serum and the synovial level decreased with declining joint infection (Yoshimura *et al*., 2020), it has been approved as a potent marker for early diagnosis of neonatal septicemia (Balayan *et al*., 2020), endotoxemia (Esmaeili Seraji *et al*., 2022). Other studies have shown that the highest SAA serum level was between 4 and 6 days of infusion of *E. coli* (Esmaeili Seraji *et al*., 2022), and it has also been used as a marker in the diagnosis of *E. coli* bloodstream infection, pre-weaning diarrhea, and mastitis (Ahmed *et al*., 2021). On the other hand, SAA could be used as a marker for differentiation of the severity of inflammation in viral and bacterial infections, as its level is higher in viral than in bacterial infections (Aydin *et al*., 2022). Mammary gland infection with *Escherichia coli*-induced mastitis (Ahmed *et al*., 2021). Accordingly, SAA serum levels could be used clinically to predict and diagnose *E. coli* infections, although it is associated with other microbial and non-microbial inflammatory conditions (Tables 3 and 4). Studies that clinically associate SAA with infections are limited and need further consideration and approval (Su and Zhang, 2022). In general, SAA can be considered a marker for inflammatory conditions, regardless of etiology.

Conclusion

To date, there are no unique specific biomarkers for *E. coli* infections. APPs can be used as markers of systemic inflammatory conditions originating from infection/inflammatory responses, regardless of the causative agent. Collectively, these patterns may aid in the early detection and prognosis of inflammatory responses. We do not recommend APPs as diagnostic, prognostic, or predictive markers for *E. coli* infection, so further studies are recommended to identify a marker for *E. coli* or other bacterial infections.

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Conflict of interest

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Authors' contributions

The authors have equal participation in conceptualization, writing the original draft preparation, writing reviews, and editing.

Data availability

All data analyzed are included in this review article.

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