# Inflammation and Biomarkers of Nutrition

**David I Thurnham**
Northern Ireland Centre for Food and Health (NICHE), University of Ulster, Coleraine, UK

## Key messages

- Inflammation is a physiological response to an injury or pathogen.
- The response is proportional to the insult.
- The response is a protective mechanism initiation by release of cytokines from monocytes and macrophages.
- A typical response is 7 to 10 days and is self-limiting.
- As part of the inflammatory response, a number of important nutritional biomarkers decline both rapidly and markedly, leading to an apparent increase in the prevalence of nutritional deficiencies, e.g., vitamin A, iron and zinc.
- Other nutritional biomarkers associated with the uptake, binding and transfer of serum iron increase during inflammation, e.g., ferritin, ceruloplasmin and lactoferrin.
- In an apparently healthy population, some of the biomarker changes can be adjusted using APP to correct the apparent nutritional status, e.g., ferritin and retinol can be adjusted to normalize iron and vitamin A status.
- In some diseases, the depression in nutrient concentration may be particularly severe and can have adverse health consequences. For example, in measles, supplements of vitamin A are recommended to overcome the metabolic depression and improve speed of recovery from the disease.
- In other disease situations, nutritional intervention is potentially harmful, e.g., iron in malaria-endemic areas and β-carotene supplements to smokers.
- In general, the changes in nutritional biomarkers associated with inflammation are transient, and concentrations will return to the pre-disease situation without nutritional intervention as the inflammation disappears.
- Chronic inflammation in response to systemic tissue damage is a feature present in apparently healthy elderly persons.
- Ways of influencing chronic inflammation through diet and / or lifestyle is an active area of research.

## Introduction

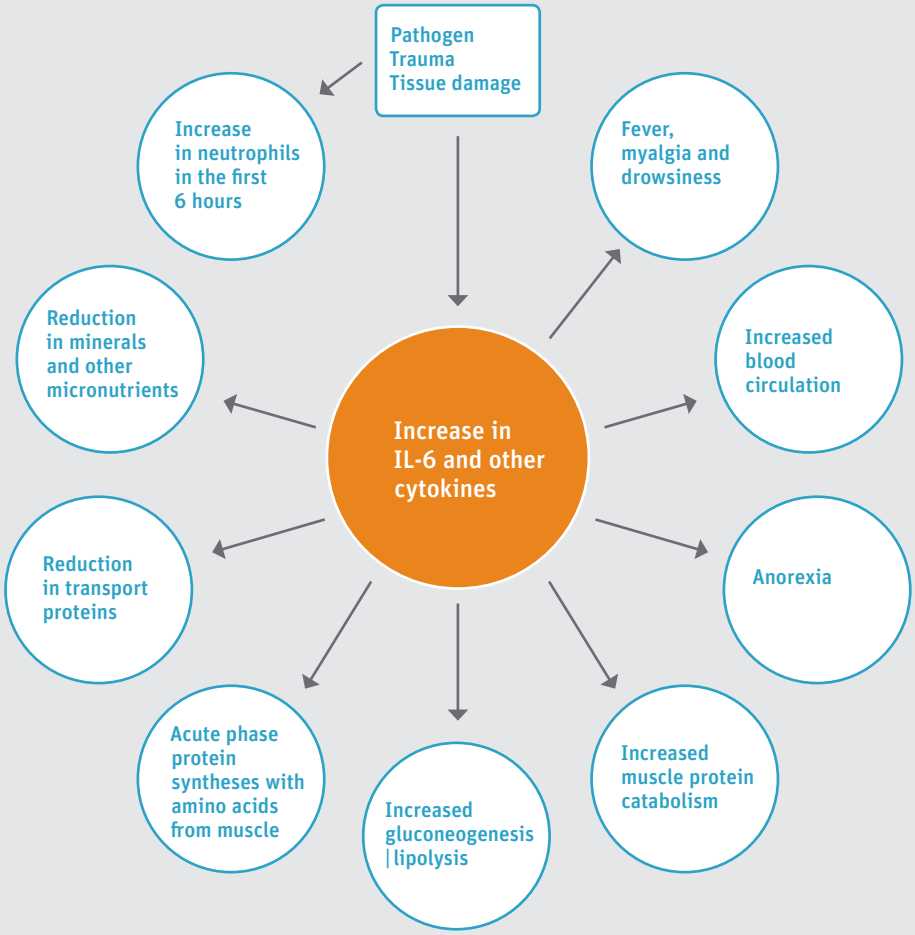
### "Feed a cold, starve a fever"

Proverbs typically date back many generations, but "feed a cold, starve a fever" may beat them all. This saying has been traced to a 1574 dictionary by John Withals, which noted that "fasting is a great remedy of fever." The belief was that eating food may help the body generate warmth during a "cold" and that avoiding food may help it cool down when overheated.[1] However, others have suggested the maxim dates back to the 14th century and that the proper phrasing should have been "Feed a cold and stave off a fever".[2] However, this is not the interpretation which has persisted in folklore into the 21st century, and it is interesting to ponder why!

Fever, of course, is a sign of acute inflammation, and the inflammatory response is a mechanism whereby the body protects itself to a greater or lesser degree from any form of trauma, whether this arises from a small cut, major surgery, bacterial, viral or parasitic infections.

> "Fever is a sign of acute inflammation, and the inflammatory response is a mechanism whereby the body protects itself from any form of trauma"

**FIGURE 1:** Some of the changes associated with inflammation following infection or trauma




We are born with an innate immune system which is exquisitely sensitive to disturbance within the body and can orchestrate an inflammatory response which is appropriate to the magnitude of a given trauma. A common feature of this response is a rapid fall in the blood concentration of several micronutrients, including iron,[3,4] zinc[4] and retinol (vitamin A).[5] The withdrawal of food from a patient would prevent any possible antagonism between food intake and the reduction in blood nutrients associated with inflammation, since any input from the diet would be minimized. Whether the metabolic role of these nutrient reductions is to conserve precious nutrients or to withhold them from pathogens, starving during fever may have unwittingly assisted recovery, and might have perpetuated belief in the proverb.

## The inflammatory response

The biochemical and physical changes in a body that are initiated in response to tissue damage or a foreign organism are termed the inflammatory or acute phase response (APR). The interaction between the body and the invader is responsible for the clinical signs and symptoms of disease: the responses begin the moment the foreign material is detected, and they expand exponentially to meet the perceived threat.[6] So fever with raised body temperature, increased blood flow through the body, anorexia, headache, cough, vomiting and diarrhea are classic symptoms of acute disease and are accompanied by a number of metabolic changes designed to assist the body to fight the invader (**Figure 1**).

The inflammatory response is typically initiated by tissue macrophages or blood monocytes.[7] Activated macrophages release a broad spectrum of protein mediators of which cytokines of the interleukin 1 (IL-1) and tumor necrosis factor (TNF) families play a unique role in triggering the next series of reactions both locally and distally. Locally, stroma cells, e.g., fibroblasts and endothelial cells, are activated to produce a second wave of cytokines that include IL-6 as well as more IL-1 and TNF. The cytokines magnify the inflammatory stimulus and potentially

**TABLE 1:** Characteristics of some well-known acute phase proteins

| Type | Acute Phase Protein | Normal serum concentration g\|L | Characteristics and response to inflammation and important properties | Time to maximum |
|---|---|---|---|---|
| **1.** Enhanced by | C-reactive protein | 0.001 | Increase 20–1000 fold | 24–48 hours |
| IL-1 and TNF[7] | Serum amyloid A (SAA) | ~0.01 | Increase 20–1000 fold | 24–48 hours |
| | $\alpha_1$-acid glycoprotein (AGP) | 0.6–1.0 | Increase 2–5 fold | 4–5 days |
| **2.** Enhanced | $\alpha_1$-anti-chymotrypsin (ACT) | 0.2–0.6 | Anti-proteinase, increase 2–5 fold | 24–48 hours |
| by IL-6[7] | Fibrinogen | 1.9–3.3 | Coagulation of blood cells and clumping | 3 days |
| | | | of bacteria. Increase 30–60% | |
| | Ceruloplasmin | 0.3–0.4 | Transport of copper and ferroxidase activity. | 4–5 days |
| | | | Increase 30–60% | |
| | Haptoglobin | 0.4–1.74[5] | Binds free hemoglobin; concentration may | 4–5 days |
| | | | appear to fall in hemolytic illness | |
| | Hemopexin | | Binds heme; only moderate increases in APR | |
| | Hepcidin: | Urine: | 6–8 fold in response to | 2 hours |
| | NB Increased by iron | Median 2.96 (IQR 0.95–6.72) | inflammation (IL-6)[46] | |
| | loading & inflammation | nmol / mmol Cr [47] | 5 fold at 24 hr in response to | 24 hours |
| | or reduced by anemia | | iron loading[46] | |
| | and hypoxia[46] | | | |

Data obtained from references[7,13,14] except where indicated otherwise. Abbreviations used interleukin (IL), tumor necrosis factor (TNF), creatinine (Cr).

prime all cells in the body with the potential to initiate and propagate the inflammatory response.

The endothelium plays a critical role in communicating between the site of trauma or infection and circulating leukocytes. IL-1 and TNF induce major changes in gene regulation and endothelial surface expression of adhesion and integrin molecules, including intracellular adhesion molecules (ICAM). These molecules interact specifically with circulating leukocytes and neutrophils, slow their flow, and initiate trans-endothelial migration into the tissue. Serum protease activity will activate the complement system which is a part of the innate immune response and helps antibodies and phagocytic cells to clear pathogens from an organism by attacking their membranes.[8] Alterations in vascular tone are early features of the APR. Dilation and leakage from blood vessels occur particularly in post-capillary venules, resulting in tissue edema and redness or increased micro-vascular permeability.[7]

Inflammatory cytokines, especially IL-6, have particularly important effects on the hypothalamus and the liver. Within the hypothalamus, the temperature set-point may be altered, generating a fever and, in the liver, there are alterations in most metabolic pathways and gene regulation to control levels of essential metabolites for defense, damage limitation and the repair of tissues following recovery. In particular the liver response is characterized by coordination and stimulation of the acute phase proteins (APP). Muscle protein catabolism is a source of amino-acids for APP synthesis and gluconeogenesis, while lipolysis of body fat supplies fatty acids to meet demands for extra energy.[9] (**Figure 1**)

Fever is one of the most common manifestations of infection.[10] It enhances host defenses and increases requirements for energy. Moderate increases in body temperature can exert a beneficial effect by increasing metabolism and the production of cells and soluble molecules needed to combat infection, since all biological and biochemical processes are speeded up by raising body temperature. Some infectious agents can even be killed by increasing temperature. However a 1°C rise in body temperature can increase basal metabolism by 10–13%[10,11] and potentially impose a major demand on body energy stores. Thus there is at the very least a transient malnutrition involving energy, protein, fat and micronutrients. The severity and the length of the infection will determine the time needed for nutritional catch-up. It is suggested that correction to nutrient stores may take four times as long to repair and increase energy and protein requirements by 30–100%.[10]

"Fever is one of the most common manifestations of infection"

The metabolic changes which occur during inflammation are short-term, catabolic, and designed to inhibit and destroy the invading organisms. However, the APR cannot be allowed to continue for more than 8 to 10 days, otherwise tissue reserves will be depleted and the body will become too weak to recover. Hence the APR comprises a sequence of self-limiting components which change from *"bullets to bandages"* as one stimulus declines and is replaced by another; or to put it another way, as the pathogens are removed and rebuilding and repair commences.

## The acute phase proteins (APP)

Since the discovery in 1930[12] of C-reactive protein (CRP) in patients with pneumonia, there has been an ever-expanding interest in the APP. The APP are a highly heterogeneous group of plasma proteins (**Table 1**) both in respect of their physicochemical properties and of their biological actions. Biological actions can include anti-proteinase activity, coagulation properties, transport functions, immune response modulation, and/or miscellaneous enzymatic activity. However, the one feature they all have in common is a role in the function of restoring the delicate homeostatic balance disturbed by injury, tissue necrosis or infection.[13]

The production of APPs is induced and regulated by the cytokines. In general, IL-6 enhances production of all APP, but CRP, serum amyloid A (SAA) and $\alpha_1$-acid glycoprotein (AGP) are specifically enhanced by IL-1 and TNF. IL-6 can also synergistically enhance their production.[7] The time course of the APPs is related to their functions: those with a role in removal of the invader are raised first, while those more involved with repair follow (**Table 1**). The pattern of the APR after elective surgery (not preceded by infection) is a rise in cortisol at 6 hours, followed by a rise in blood leukocytes which peaks at 10 hours. There appears to be a delay of about 6 hours before any rise in the APP occurs. CRP, SAA and $\alpha_1$-antichymotrypsin (ACT) activity increase rapidly and peak around 48 hours, while most of the others peak later (**Table 1**).[14] Most APP increase in concentration in response to trauma or infection but there are four negative APP where concentrations fall following trauma: retinol-binding protein (RBP), transthyretin, transferrin and albumin (**Table 2**). As these are also nutritional biomarkers, they are dealt with in the next section.

## Biomarkers of nutrition

Infection and nutrition are intimately linked.[10] The demands on energy to fuel the inflammation and provide amino acids for the *de novo* synthesis of the many APPs are described above. In addition, rapid and large changes in the serum concentrations of a number of nutrients that are used as nutritional biomarkers occur. The speed and amount of change are more likely to indicate direct effects of the APR on metabolism rather than indirect effects such as hemodilution and vascular changes induced by the inflammation. Serum retinol,[15,16] iron,[3,4] ferritin,[17] zinc[4] and 25-hyroxycholecalciferol (vitamin D)[18] concentrations change by 40% or more in the 48 hours following infection or trauma. The concentrations of most nutritional biomarkers decrease, and where changes in concentration are small, e.g. 10%, then the increase in microvascular permeability is probably mainly responsible. The increased leakiness of the vasculature is probably responsible for most, if not all, of the fall in transferrin and albumin concentrations,[14] and possibly also transthyretin. The liver RBP production, however, is definitely depressed by endotoxin,[19] and the serum concentration falls in a similar way to that of retinol.[14–16] Ferritin, ceruloplasmin and lactoferrin are the exceptions to the other nutritional biomarkers since concentrations increase. The rate of increase in ferritin is comparable with that of CRP, SAA and ACT (**Table 3**).

> "Infection and nutrition are intimately linked"

## Interpretation of nutritional status in the presence of inflammation and infection

### *Covert inflammation*

Inflammation can be present both in apparently healthy and in sick people. In the absence of overt disease, inflammation is usually mild, but nutritional biomarkers are still altered (**Table 3**)

**TABLE 2:** Negative acute phase proteins

| Acute phase protein | Abbreviation, other names | Normal serum concentration g/L | Characteristics | Time to maximum effect |
|---|---|---|---|---|
| Albumin | Alb | 35–45 | | |
| Transferrin | Tf | 2–3 | All proteins: | |
| Thyroxin-binding protein | Pre-albumin, transthyretin | 0.3–0.4 | Decrease 30–60% | 24–48 hours |
| Retinol-binding protein | RBP | 39–45 mg/L | | |

**TABLE 3:** Nutritional biomarkers influenced by inflammation

| Serum biomarkers: unless otherwise indicated | Direction of change[#] | Acute response (24 to 48 hours) % | Chronic or long-term response (3 to 10 days) % | Reference |
|---|---|---|---|---|
| Retinol | – | 40–70 | 10–15 | 15, 16, 20, 48 |
| Retinol-binding protein | – | 40–70 | 10–15 | 15, 16, 20, 48 |
| Carotenoids | – | 20–50 | 40–60 | 33, 49-51 |
| Zinc | – | 70 | 10–15 | 4 |
| Iron | – | 50 | | 4 |
| Ferritin | + | 100% or more | 100% or more | 17 |
| Transferrin receptor | (–) + | Small fall | ~50 increase | 52 |
| 25-Hydroxy-cholecalciferol | – | 40 | 20–30 | 18 |
| Pyridoxine | – | No information | Negative association with inflammation | 53, 54 |
| Selenium | – | No information | 40–60 | 55 |
| Leukocyte ascorbic acid | – | ~40 | Normalized in 5 days | 56 |
| Vitamin C | – | Little effect | Variable fall | 55 |
| Hemoglobin | – | Little effect | 5–10 | 52 |
| Albumin | – | 10–15 | 10–15 | 14 |
| Transferrin | – | 10–15 | 10–15 | 14 |

[#]Signs indicate the direction of change '–' fall and '+' increase.

and do not reflect true nutritional status. Hence we developed methods using CRP and AGP concentrations to characterize the type of inflammation and adjust serum retinol and ferritin concentrations with correction factors to improve the assessment of vitamin A and iron status.[20,21] In the absence of overt disease, people with inflammation are generally in convalescence[22] and require nutritional supplements to restore the body's nutritional reserves.

### *Overt inflammation*

In people who are sick, it is more difficult to generalize. It is important to understand the reasons for the changes in the biomarkers produced by the trauma in order to interpret nutritional status and know whether it is appropriate to supplement with nutrients or not. The reasons for the changes may differ as illustrated by vitamin A and iron. In some cases, interpretation and intervention may depend heavily on nutritional status prior to infection.

In the case of vitamin A, we previously showed that the depression in plasma retinol concentrations by malaria in urban and rural Thai adults was similar – a difference of approximately 0.6 µmol/L between the means of the controls and respective patient groups.[23] However, concentrations of retinol in the control subjects in the rural community were significantly lower than those in the urban adults, so depression of retinol by malaria in the rural adults produced many more patients with dangerously low retinol concentrations than in the urban group. However, there is no evidence that the risk of vitamin A deficiency is increased in people with malaria, therefore there would seem to be no case for supplementation with vitamin A. The depression in serum retinol produced by malaria is transient and reversible on recovery and, as far as we know, it does not affect recovery from the disease.

In the case of measles, however, there are reports from Africa, India and SE Asia that measles was associated with a high risk of xerophthalmia and blindness.[24,25] Measles is a viral disease which strongly depresses retinol concentrations and damages epithelial tissues.[24,26] Several groups showed that vitamin A supplements provided enormous benefits for the treatment of, and recovery from, severe measles.[27,28] Hussey and Klein[28] also showed that the benefits of vitamin A in measles prevailed in spite of the fact that vitamin A deficiency almost never occurred in the region served by their hospital. Thus in measles cases it is possible that the damage caused to epithelial tissues exceeds any potentially protective effects from the reduction in plasma retinol. Vitamin A supplements are now recommended as part of the treatment of measles even in developed countries.[29]

> "Vitamin A supplements provide enormous benefits for the treatment of severe measles"

Sick boy at Kakuma refugee camp, Kenya

However, vitamin A supplements in the form of β-carotene are not always without harm. Smokers have an increased risk of lung cancer, and several prospective studies have shown them to have low plasma β-carotene concentrations.[30] However, two β-carotene supplementation studies in smokers in Finland and the USA were associated with increased rates of lung cancer.[31] There is evidence that smokers have mildly elevated CRP concentrations[32,33] but we do not know what advantages low β-carotene concentrations confer, and supplements did not reduce human cancer rates as had been expected.[34] Did the antioxidant β-carotene supplements accelerate development of pre-existing cancers?[35]

Although there is a very obvious difference in the demography of the measles and lung cancer scenarios, it does not follow that nutritional supplements in poor communities will always be beneficial and those in developed countries potentially harmful. Low iron status is associated with impaired cognition and poor growth, but in the presence of inflammation it may be protective, particularly in countries where malaria is endemic. Malaria is caused by a parasite which destroys red cells, causing severe anemia and death. However, attempts to correct the anemia and improve iron status with iron supplements have worsened the situation. Oppenheimer showed that iron dextran given *i.p.* to improve iron status in 2-month old infants in Papua New Guinea was associated with more severe malaria,[36] and a trial giving iron supplements to children in Pemba[37] had to be stopped, as there was an increase in hospital admissions in those children receiving the iron. The adverse effects of iron may be because hemoglobin released from lysed red cells will potentially oxidize and damage tissues. The APP haptoglobin will scavenge hemoglobin, but in malaria-endemic communities, production of haptoglobin is often insufficient. Providing more iron from supplements increases this potential damage.

Diseases, epidemics and fevers have been a scourge of mankind over the last 500 years and doctors were generally impotent to intervene. The only treatments available were dietary, leeches to increase anemia, and other remedies that made the human body less attractive to the invading pathogen. *"Starving the fever"* may have increased the chance of recovery.

### Ageing and chronic inflammation in apparently healthy elderly people

One of the research areas which has perhaps received too little attention is the etiology of chronic inflammation in the elderly and how to minimize, delay or prevent the increased risk of disease that accompanies inflammation. There is evidence that the lifestyle is an important factor in determining the risk of chronic inflammation and disease. Diet is a significant part of lifestyle, and dietary factors have been implicated in the risk of coronary heart disease (CHD), cancers, age-related macular disease (AMD), and others. Dietary excesses are implicated in obesity and alcoholism, and these increase the risk of non-communicable diseases such as diabetes, cancers and cardiovascular disease.

Our innate immune system is designed to detect foreign material entering the body, but it will also respond to damaged cellular and tissue components generated endogenously. Oxygen is essential for life but oxidation will generate free radicals, potentially causing tissue damage. Endogenously sited antioxidant enzymes and antioxidant nutrients repair and minimize the effects of oxidation, but these protective mechanisms may be overwhelmed by external factors. Smoking and obesity are two such external factors that increase oxidative stress and potentially overwhelm the body's antioxidant defenses. Inflammatory changes initiated from endogenously generated damage may need to be considered differently to the typical acute phase response.

"Our immune system is designed to detect foreign material entering the body, but it will also respond to damaged cellular and tissue components generated endogenously"

Age-related macular degeneration (AMD) is a leading cause of blindness in all populations of European origin.[38] The pathogenesis of AMD is not well understood, but a hallmark of early disease is the appearance of drusen deposits, which accumulate in the space between the retinal pigment epithelium and Bruch's membrane in the eye. Studies on the molecular composition of drusen have implicated inflammation and particularly the local activation of the alternative pathway of the complement cascade in the retina.[39] The complement system plays an important role in the defense against microbial pathogens by the classical stimulation route by external factors,[40] but there is also a mechanism whereby systemic activation through the alternative pathway can occur and is implicated in the pathology of AMD.[40,41] Raised concentrations of pathogenic complement end-products in the blood of patients with early AMD is further evidence of acute activation of the alternative pathway. The macula contains a high concentration of the xanthophyll carotenoids, lutein and zeaxanthin, which should reduce the risk of oxidative damage, but efficiency of this system may be compromised as people age for a number of reasons, including poor diet, smoking and obesity.[42] Interestingly, lutein supplements have recently been shown to markedly decrease circulating concentrations of complement end-products in the blood of patients with early AMD, and the authors suggest that such supplements may provide a simple method to control the inflammatory pathway of the innate immune system.[41,43]

Changes to biomarkers of the complement cascade have also been shown to accompany Alzheimer's disease[44] and may be a component in other neurological diseases, e.g., Parkinson's and multiple sclerosis. Inflammatory changes initiated systemically, especially in the brain, may be difficult to detect by blood biomarkers, and reversing or alleviating the effects of the disease may be even more difficult to achieve by dietary supplements. Inflammatory changes may, however, be early biomarkers of systemic damage in the tissues. Such changes may be reversible in the early stages by alterations to lifestyle and diet, but more research is needed to better understand the impact of inflammation on the etiology of the non-communicable diseases and how lifestyle may influence them.

> "More research is needed to better understand the impact of inflammation on the etiology of the non-communicable diseases"

## Conclusions

Inflammation is an innate protective response to assist the human body to overcome an infection or repair tissue damage. The response is initiated by the release of cytokines from stimulated macrophages and is proportional to the level of the disturbance. The response often includes a rise in body temperature, increased blood flow, anorexia, and catabolism of muscle protein and body fat. The latter provide the amino acids and fatty acids for extra energy and the synthesis of APP. Transient reductions in the serum concentrations of many nutritional biomarkers accompany the many metabolic changes and make assessment of nutritional status difficult, but if there is no overt evidence of disease, changes in the concentrations of CRP and AGP can be used to improve the assessment of vitamin A and iron status. However, in the presence of disease, status cannot be easily assessed. Furthermore, the nutrient reductions can be harmful, as in the case of measles, where the disease increases the risk of xerophthalmia and vitamin A supplements have proven benefit in treatment. Yet nutrient supplements in people with inflammation can increase disease risk, as in the case of β-carotene and iron. Chronic inflammation in response to systemic damage is a particular feature in the elderly and increases the risk of non-communicable diseases such as cancer, heart and neurological diseases. Methods to reduce chronic inflammation in apparently healthy elderly people is an active area of research.

**Correspondence:**
***David I Thurnham,*** *46 High Street,*
*Little Wilbraham, Cambridge, CB21 5JY, UK*
***Email:*** *di.thurnham@ulster.ac.uk*

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