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Relation between nutrition and immunity

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Abstract
For survival, a well-functioning immune system is critical. The immune system must be constantly alert, monitoring for signs of invasion or danger and make backup for response. To distinguish self from non-self and furthermore discriminate between non-self-molecules which are harmful (e.g., those from pathogens) and innocuous non-self-molecules (e.g., from food) cells of immune system play a important role altogether. In this article of Nutrients explores the relationship between diet and nutrients and immune function. Here, we outline the key functions of the immune system, and how it interacts with nutrients across the life course, highlighting the work included within the body. This includes the role of macronutrients, micronutrients, and the gut microbiome in mediating immunological effects. Nutritional modulation of the immune system has applications within the clinical setting, but can also have a role in healthy populations, acting to reduce or delay the onset of immune-mediated chronic diseases. Upcoming research in this field will ultimately lead to a better understanding of the role of diet and nutrients in immune function and will facilitate the use of bespoke nutrition to improve human health.

Keywords: Nutrition, immunity, macronutrients, micronutrients, microbiome, life course, probiotic, prebiotic, inflammation

Introduction

The immune system accounts for a relatively minor portion of total nutritional requirements in the normal healthy animal but activation of the immune system in response to an immune challenge has a major impact on nutritional status and requirements for most nutrients.

Nutrient deficiencies increase susceptibility to most infectious diseases, including bacterial, viral and parasitic diseases. Once disease has developed, nutritional deficiencies increase the severity of the disease and increase the probability of secondary infections. Deficiencies of vitamins or trace minerals significantly depress immune function and resistance to stress even when animals are otherwise well fed with sufficient energy and protein.

Stress such as handling, transportation, transition, that during peri parturition period, physical trauma, surgery, general infection, haemorrhagic bowel syndrome, fatigue, fasting, and unfamiliar environment etc increases requirements of many nutrients essential for immune function and leads to multiple short term nutrient deficiencies. Consequently, nutrition has the largest impact on morbidity and mortality in stressed animals. For example the immune system is suppressed in stressed cattle, contributing to the high incidence of respiratory disease in the first 45 days on feed after transportation. Some nutrients such as vitamin E can be fed at levels above normal requirements to stimulate immunity of immuno suppressed animals.

All animals require energy, amino acids, fatty acids, fat soluble vitamins (A, D, E, K), water soluble vitamins (B-vitamins), trace elements and macro minerals for both health and growth. When availability of any of these nutrients is limited, deficiency symptoms occur most quickly in tissues with the highest rates of protein synthesis or metabolic activity. The immune system is particularly sensitive to a nutrient deficiency because any immune response requires rapid synthesis of proteins for immune cells and immune products. Most nutrient deficiencies including vitamins and trace minerals directly or indirectly affect synthesis of these proteins. Other nutrients regulate the immune response (vitamins A and D), or act as antioxidants to protect immune cells and other cells from the toxic effects of a wide variety of enzymes and chemicals used by the immune cells to destroy bacteria and infected cells. Compared to other systems in the body, the immune system has especially high requirements for antioxidant nutrients but these nutrient are quickly depleted when animals are stressed.

At every stage of the immune response, specific micronutrients, including vitamins and minerals play a key role and often synergistic, and the deficiency of only one essential nutrient may impair immunity (Barrea *et al*., 2020) [1].

Nutrition has the greatest impact on immunity during stress. It can be difficult to get enough nutrients into cattle, particularly those that need it the most. Nonetheless, proper nutrition during immune function directly, and also indirectly by improving resistance to stress. Providing key nutrients can reduce stress-induced weight loss and immunosuppression, improve weight gain and reduce morbidity and mortality from stress induced immune challenge such as during that of bovine respiratory disease.

Adequate and appropriate nutrition is required for all cells to function optimally and this includes the cells in the immune system. An "activated" immune system further increases the demand for energy during periods of infection, with greater basal energy expenditure during fever for example (Childs *et al*., 2019) [5].

Analysis of nutrition and immunity in animals other than humans, especially invertebrates, has introduced newer discoveriesand insights. As a rich source of macromolecules and nutrients,earthworms have long been used as food among various indige-nous cultures. The nutritional and medicinal value of earthwormshas been utilized for centuries among traditional and comple-mentary practices (Cooper *et al*., 2017) [6].

Background: What is Immunity to Infection?

Animals resist infection using non-specific mechanisms (innate' immunity) and specific mechanisms (acquired immunity). Almost all immune mechanisms are less effective in stressed animals.

Innate immunity

- Innate immunity includes:
- Epithelial tissue which covers body surfaces – ex. skin or hide, hoof, cornea
- Epithelial tissues lining body cavities –ex. respiratory, urogenital, gastrointestinal tract. Theses epithelial lining cause a physical barrier to keep infectious agents away from entering the body. Breaks in this covering layer caused by physical damage or by nutrient deficiencies such as vitamin A and zinc can result in infectious agents gaining access to the body.
- Secretions that block infectious agents and numerous antimicrobial compounds in body fluids and secretions frequently affected by stress – ex. Mucus
- Secretions that wash out infectious agents, and numerous antimicrobial compounds in body fluids and secretions; frequently affected by stress-ex. saliva, tears
- Cells in blood and tissue that engulf, kill and digest infectious microorganisms. These are called phagocytes and include macrophages, monocytes, and neutrophils. They continually circulate through blood and migrate into tissues in search of invading pathogens. This important defence is seriously impaired by stress.
- Receptors on the surface of these cells which recognize and bind to pathogens.
- Signalling molecules (e.g., chemokines, cytokines) which communicate sites of infection and regulate expression of immune genes.
- Normal microbial flora which can compete with disease causing organisms, thereby holding them in check; is less effective in stressed animals.

Specific or acquired immunity

Exposure to a foreign substance (antigen) results in the development of immune cells and antibodies specific against that particular antigen only. Specific immunity takes time to develop, and therefore is effective in preventing infection only if the animal was previously exposed to that antigen. It is also important for recovery from many infections. The foreign substance (antigen) may be a live virus or bacteria but does not have to be infective or alive to induce immunity. Weakened or dead viruses or bacteria, and even specific fragments of pathogens or pieces of their DNA can be used in vaccines to induce immunity with reduced risk of disease. Exposure to the antigen triggers growth and development of two types of blood cells specific for eliminating the antigen. These are the T-cells (responsible for cell-mediated immunity) and the B-cells responsible forantibodyproduction (humoral immunity).

T-cells secrete numerous hormones (such as interleukins and interferon) which up regulate or down regulate the entire immune system as needed, and increase effectiveness of other immune cells including phagocytes and B-cells. In addition, some T-cells directly destroy target cells. Antibodies are fairly large proteins that are secreted by B-cells and found in blood plasma, nasal secretions and other fluids. Because of their size, they cannot enter into bovine cells so are not effective against intracellular pathogens. All antibodies act by binding to the foreign substance. In many cases, this prevents the virus or bacteria from replicating or being infective, but also makes it much easier for other immune products or cells to destroy the pathogen. Vaccines may be designed to stimulate primarily an antibody response or an increase in cell- mediated immunity, depending on which type of immune response is most effective against a specific pathogen.

A nutrient deficiency does not affect all immune mechanisms equally, nor does it always affect the same mechanism equally for different antigens. A group of deficient animals may have adequate antibody responses to some antigens (or vaccines), and depressed antibody responses to other antigens. Similarly, under practical conditions, deficient animals may be more susceptible to some but not all disease causing organisms.

Nutritional Requirements of Stressed Animals

Acute or prolonged stress makes animals more susceptible to disease by increasing levels of hormones which suppress the immune system and by depleting nutrients critical to an effective immune response. Stressful stimuli in cattle include handling, transport, physical trauma, fatigue, fasting, and unfamiliar environment etc. These induce hormonal responses which control and alter animal metabolism. Cortisol, epinephrine, nor epinephrine, aldosterone, beta-endorphin, and enkephalins are released in large amounts in response to stress. A short-term stress may have relatively minor effects on metabolism and nutritional status. A long-term, chronic stress may cause substantial metabolic changes. Metabolic changes during stress are designed to control and reserve energy and other nutrients for use in the most vital processes needed to combat the stress. Metabolic pathways shift from anabolic processes (growth) to primarily catabolic (tissue breakdown of proteins and fat).

The first response of any category or any species of stressed animal is drop in feed intake. Stressed animals have higher nutritional requirements, but do not consume as much feed as unstressed animals. Feed intake is the foremost nutritional problem for highly stressed loads of cattle. The first objective is to get enough feed into the animal so that it can stop breaking down its own tissues for fuel and begin to eliminate nutrient deficits. Cattle produce blood glucose essential for the central nervous system and red blood cells by breaking down body proteins in liver, kidney, intestine, and skeletal tissue to provide glucose precursors. Body fat is broken down to provide fatty acids, the primary energy source for most other tissues. These free fatty acids can be converted to ketone bodies, primarily ß-hydroxybutyric acid and acetoacetic acid, which can lead to a metabolic acidosis. The nutrient concentration of the diet has to be increased to compensate for the low intake. Stressed cattle are often deficient in energy, amino acids, vitamin A, B-vitamins, calcium, phosphorus, potassium, magnesium, zinc, and copper (Nockel, 1990) [14]. Antioxidant requirements are markedly increased by both stress and disease, because both result in accelerated production of highly reactive oxygen by products, peroxides, and free radicals. Free radicals damage healthy tissues. Antioxidants such as vitamin E and vitamin C are quickly depleted in stressed animals, particularly in the white blood cells where they are critically important for immune function. Antioxidants scavenge free radicals thereby, checking tissue damage by them.

Stressed, previously fasted cattle differ from normal cattle in ability to utilize certain feeds and nutrients because of changes in rumen function. Stressed cattle such as calves have a lower tolerance for non-protein nitrogen (e.g. urea) than normal calves, which should be limited to 30 grams or less per day during the first 2 weeks of feeding. Stressed calves also have a low tolerance for dietary fat, and for silage compared to non-fermented feeds. Feed intake, gain, and immune function are improved when stress calves are fed sufficient undegradable intake protein UIP). There is some indication that stressed calves may differ from normal cattle in having some bypass of soluble nutrients that are normally completely degraded in the rumen by bacteria. If so, it may be possible to take advantage of reduced ruminal function in the first 1-2 days on feed to supplement nutrients such as glucose, choline, ascorbic acid, and various B-vitamins when these requirements are known.

Effects of Disease on Nutritional Status

Infection results in a complex array of metabolic responses which affect the nutritional status of the animal. Feed intake decreases more than 50% in cattle with respiratory disease and fever, and takes 10 to 14 days to return to normal. During this time, requirements of virtually all nutrients increase, even though nutrients are deflected from growth to immunity. Proteins must be synthesized for the immune response, development and resolution of fever, and repair of cell and tissue damage.Body proteins are broken down to provide energy and amino acids for the immune system. Losses of important minerals such as magnesium, potassium, phosphate, and zinc are also increased. .

Immune activation increases requirements for antioxidant nutrients, trace minerals, and vitamins similar to the effect of stress. Stress aggravates or predisposes animal to immune challenge. Consequently, when cattle are stressed before an immune challenge, nutrients critical to the immune response are likely to be in short supply. Trace minerals and B-vitamins are required as co-factors for the chemical reactions involved in breaking down body tissues and synthesizing new proteins. The major extracellular electrolytes, sodium and chloride, are influenced by hormonal changes. Urinary excretion of salt may increase during the onset of infection, and may lead to dehydration. The kidneys may then begin to retain body salt and water. Diarrhoea can result in substantial direct faecal losses of sodium, chloride, bicarbonate and potassium.

Effect of Nutritional Status on Resistance to Infection

Good nutrition improves disease resistance of stressed cattle, by helping to counteract the suppression of the immune system caused by stress hormones and by providing nutrients essential for maintaining and activating the immune system as required.

Energy: Stressed calves seem to have an altered eating pattern—unlike normal calves, they won‘t eat more of a lower energy diet, and given a choice, they select a diet with about 72%. Consequently, performance of lightweight stressed calves is increased with high-concentrate receiving diets (>60% grain) but morbidity rate may increase as well. Generally morbidity and severity of illness increase with increasing grain in the diet. The optimum concentration of grain in the receiving diet depends on the age and weight of animal, previous management, stress level, and other factors; cattle with lower intakes (calves) can safely consume diets with a higher proportion of grain than can cattle with higher intakes (yearlings).

Protein: *D*iets that contain relatively low or high levels of dietary proteins adversely affect immunity to infection compared to diets with moderate protein levels (Galyean *et al*., 1999) [9]. Morbidity rate has been found to be lowest for diets containing 12 to 14% protein, and increased as protein increased to 22% of DM. However, the best performance is usually achieved at higher levels of dietary protein (16 to 20%). Morbidity was better when less soluble, higher bypass proteins were fed (distillers dried grains, blood meal). Nissen *et al*.,1989 [13] reported that gain and feed efficiency improved as metabolizable protein concentration increased but serum cortisol increased linearly, and the proportion of calves responding to the IBR vaccine decreased linearly.

Vitamins and minerals: Vitamins and minerals, such as Vit A, vitamin E, selenium, copper, Chromium and zinc, when properly supplemented, can enhance a cow‘s immunity against diseases, such as mastitis, by increasing resistance to infections and by decreasing severity of infections when they do occur. Cow requirements for vitamins and minerals are influenced by several factors, including age, stage of pregnancy, and stage of lactation. For some vitamins and minerals, the amount required for optimal immune response is greater than the amount required for growth and reproduction. Cattle can have sufficient vitamin and mineral intake for adequate growth and reproductive performance but not have optimal immune performance. By the time clinical signs of deficiency become apparent, immunity, growth and fertility already may have been compromised.

Vtamins: Vitamins A and D within the ranges that are normally fed, are important in regulating immunity. Vitamin A deficiency reduces resistance to all types of disease, including parasites. Vitamin A supplementation is essential for cattle fed grain based diets. In ruminants, for example, supplementation with β-carotene at dry-off reduced mammary gland infections (Chew, 1987) [4]. β-carotene increased lymphocyte blastogenesis (Daniel *et al*.,1990) [7] and increased neutrophil killing activity (Michal *et al*., 1994) [12]. Under practical conditions, vitamin D deficiency is unlikely to be a concern even when cattle are not supplemented, unless they also do not have access to sunlight.

Atioxidant nutrients are crucial to the immune response, becoming rapidly depleted during infection. These key nutrients include dietary antioxidants such as carotenes, vitamin E, and vitamin A, and trace minerals such as selenium, zinc, copper, and manganese used to synthesize antioxidant enzymes Antioxidants protect immune cells and surrounding tissue from damage caused by the immune response, which otherwise would damage the animal as much or more than the disease organisms. Antioxidants are particularly important for the effectiveness of phagocytes, which are the front line of defence against invading pathogens. If phagocytes are deficient in antioxidants, microbial killing is ineffective. Vitamin E is currently the most important antioxidant in diets. Vitamin E and Se play overlapping and essential roles in support of the immune system in ruminant animals.

Vitamin E supplementation increases lymphocyte proliferation (Reddy *et al*., 1986) [16]. Supplementation with vitamin E has improved growth, feed efficiency, morbidity, and antibody titres of stressed cattle, but not consistently. In studies with dairy calves, vitamin E supplementation decreased ($P< 0.05$) serum cortisol concentrations, an indicator of stress. Dietary vitamin E in excess of requirements for growth increases resistance to stress and disease. The vitamin E status of the cattle, exposure to stress and disease, and other factors may influence the response. supplementation with vitamin E decreases the incidence of mastitis, and selenium decreases the duration of these infections. Combining the two supplements results in the greatest increase in defense against mastitis. Deficiencies of vitamin E and selenium also have been found to increase the incidence of retained placenta.

B-vitamins and vitamin C affect immunity and resistance to stress.Rumen microbes can synthesize B vitamins. Production of B-vitamins by rumen microbes is directly related to energy availability in the rumen; synthesis of vitamin C in the animal is directly related to energy availability in animal tissue. The combination of stress and low intake can result in low availability of B-vitamins which may affect rumen microbes and/or the animal itself. B-vitamin supplementation of receiving diets has improved performance and reduced shipping fever in several studies. In a study at Kansas, B-vitamin supplementation in combination with vitamin E tended to improve gain and significantly improved feed efficiency, without significantly affecting morbidity. Vitamin B_{12} deficient lambs had higher fecal egg counts than vitamin B_{12} supplemented one after natural infection with gastrointestinal nematodes.

Magnesium and phosphorus are the most important macro minerals associated with the immune response; their supplementation levels have influenced mortality in other animal species but have not been studied in this regard in cattle.

Trace mineral supplementation: It is important for maintaining resistance to infectious disease. Trace minerals have numerous functions as components of vital proteins. Young growing animals are depositing protein at high rates and are therefore more vulnerable to trace element deficiencies than older animals. Copper, zinc, manganese, and selenium are required for the production of antioxidant enzymes. Feeding elevated levels of Se to ruminant animals reduces incidence of diseases (including intra-mammary infections. For example, Hogan *et al*. (1990) [8] reported that Se enhanced neutrophil killing activity. Maddox *et al*. (1999) [11] have reported that Se deficiency increases neutrophil adherence and altered adherence could affect ability of neutrophils to attack and sequester pathogen. Cao *et al*. (1992) [3] reported that Se and vitamin E increased antibody responses of dairy cattle. In a more recent study, Parnousis *et al*. (2001) [15] reported that injection of Se either alone or in combination with vitamin E significantly improved the production of specific antibodies against *E. coli*, and that the production of specific antibodies was greater after the administration of Se alone. Selenium deficiency can increase the incidence of embryonic death and uterine infections and can decrease fertility. Deficiencies of copper and selenium impair the ability of bovine phagocytes to kill invading microorganisms. Cu supports immunity as it is associated with many proteins. Deficiencies of copper also have been associated with retained placenta, embryonic death, and decreased conception rates. Inadequate copper status may be related to an increased incidence of infections at calving. Cu increased neutrophil killing activity of a common mold: *Candida albicans*. Ward *et al*. (1997) reported that Cu enhanced cell mediated immunity (DTH-response). Zinc is also an integral part of the immune system. Zinc is important for production of keratin, which lines the inside of the teat duct and helps to keep out micro-organisms that can cause mastitis. Zinc deficiencies also will delay sexual maturity and may also cause fetal abnormalities. A zinc deficiency increases nonspecific infections, and inhibits normal healing of wounds. Supplementation with zinc or with high levels of trace minerals has improved recovery from respiratory disease in several studies. Zinc- build up a successful immune response against gastrointestinal nematodes.

Although chromium is depleted in stressed animals, and chromium supplementation has improved immune function in some studies, more information is needed to determine when supplementation would be cost-effective. Several studies have indicated that supplementation of Cr to dairy cattle, in a biologically-available form (*e.g*., Cr-amino acid complex or Cr-yeast), benefits immunity. Supplementation of organic Chromium to transit- stressed calves and early lactation dairy cows, improved the immune status and milk production. Chromium seems to reduce blood cortisol concentration during stress and promoted insulin or insulin like growth promoter sensitivity in target tissues such as muscle, mammary gland and immune system. Improved performance and lower disease occurrence can be found.

Iron supplementation: meet the loss through blood during gastrointestinal parasitic infections *(Koski and Scott, 2003).*

Mo in diet containing 4-8 mg/kg DM in sheep reduces worm burden *(McClure et al., 1999).*

Organic iodine is extensively used for foot rot control at levels exceeding those required for growth. Young, growing cattle may be most susceptible to footrot.

Suggested Feeding Levels in Total Diet

- Vitamin E: 1000 IU/day for dry cows, 500 IU/day for lactating cows
- Selenium: 0.3 ppm
- Copper: 20 ppm
- Zinc: 40-60 ppm

Additionally, Omega-3 and Omega-6 fatty acids, Feed additives, Bypass protein etc. have been shown to improve immunity against various diseases.

Omega-3 and -6 fatty acids (ω-3 and ω-6). Dietary fatty acids can affect immunity through the production of the cytokines (Lessard *et al*., 2003) [10]. A mechanism by which fatty acids affect immunity is through production of eicosenoids (*e.g*., prostaglandins) and leukotrienes. Diets rich in the ω- 6 fatty acids, such as linoleic acid (C18:2), lead to the formation of arachidonic acid; whereas diets rich in the ω-3 fatty acids (such as linolenic acid, C18:3, flaxseed, and fish oils) lead to the formation of, for example, eicosapentaenoic acid (EPA). Eicosenoids synthesized from arachidonic acid tend to have strong inflammatory potential; whereas those synthesized from EPA have lesser potential. Hence, feeding fatty acid mixtures which are enriched in the ω-3 fatty acids reduces inflammatory reactions and reduces production of pro inflammatory cytokines including IL-1, IL-6, and TNFα.

Changes in nutritional status have a wide range of effects on the body, which can influence organ size, hormone, and cytokine levels, and immune cell populations and function. This link between nutrition and immunity is mediated, in part, by a select group of adipocytokines, such as leptin, which can influence immune cell number and function through its effects on cellular metabolism (Alwarawrah *et al*., 2018) [1].

Feed additives-fungus

Fungi: Feeding of fungi such as *Duddingtonia spp.*, *Harposporrium spp*. and *Arthrobotrys spp.* as a feed additive control gastrointestinal parasite.

Probiotics: such as lactobacilli and bifidobacteria, yeast culture (*saccharomyces spp.)* helps to improves growth rate and feed conversion efficiency in calves, microbial protein flow and DM intake, particularly in poor managemental conditions.

Prebiotics: Such as Lactulose, lactilol, a variety of oligosaccharides and inulin Prebiotics have shown promise in the prevention and control of exogenous and endogenous intestinal infections and good health of the animals.

Feeding By-pass protein: Improves resistance and expression of immunity to gastrointestinal parasites and increase the resistance of sheep to *Haemonchus contortus.*

Beneficial Effects of Nutrients in Excess of Growth Requirements

Several nutrients such as vitamin E and selenium enhance immunity above normal levels when fed in excess of requirements for growth. These same nutrients stimulate immunity when immune function is below normal, as in animals that are stressed. Some nutrients such as vitamin E and chromium influence production of stress hormones such as cortisol. Antioxidant nutrients in general, including vitamin E and selenium, also reduce the susceptibility of cells throughout the body to the cortisol that is produced in response to stress. Vitamin E is depleted in stressed cattle whereas vitamin E supplementation appears to counteract stress-induced immunosuppression (see vitamin article). A small excess of selenium may also be beneficial.

Optimal immunity

The immune system appears to have priority for nutrients over growth. Immune activation is costly. Resources devoted to immune activation cannot be used for growth. As a result, any immune response will depress growth rate and feed efficiency. The optimum immune response is the one that is the shortest in duration and the lowest in intensity while successfully eliminating the pathogen. An extreme immune response not only wastes resources but may cause local cell damage and depress productivity. Reducing challenges to the immune system by providing a clean environment and reducing stress can improve growth rate. In normal healthy cattle, there is a trade-off between growth and immunity – both cannot be maximized at the same time. This is not usually a practical concern because the immune system functions very well at nutrient levels ideal for growth. Some very promising research has been done in this area but much more is needed to evaluate products and economics of use. However, cattle feeders dealing with less than ideal facilities or management, limited labour, or lightweight, high risk cattle may prefer to sacrifice some growth but reduce disease risk by adapting cattle to full feed more slowly than usual. This can reduce the incidence of respiratory disease, death loss, and medical costs during the receiving period.

Balancing diets for immunity

Rations of stressed animals should be adequately supplemented with trace minerals, vitamin A and vitamin E. Feeding higher levels than normal of these nutrients in the receiving period can compensate for reduced intake and marginal deficiencies. In order of priorities, providing a palatable diet and encouraging feed and water consumption is most important. There is little benefit from adding expensive nutrients to an unpalatable diet. In situations where the cattle are most vulnerable to disease (high stress, younger animals, poor environmental conditions, etc.) and the disease risk is high, supplementing high levels of nutrients such as vitamin E during the receiving period may improve gain and reduce morbidity substantially. A large number of nutrients have shown promise for improving feeder calf health, including chromium, zinc methionine, B-vitamins, vitamin E, HMB, After cattle have recovered from stress-induced immuno suppression and are adapted to the finishing diet, balancing diets to meet requirements for growth usually provides adequate nutrients for immune function.

Conclusion

In this article the study is conclusive that Nutrients, the collected works provide a breadth of reviews and research indicating the key influence of nutrients and nutrition on immune responses in health and disease. Nutrients may impact directly or indirectly upon immune cells causing changes in their function or may exert effects with changes in the gut microbiome. A better understanding of the role of nutrients in immune function will facilitate the use reliable and appropriate nutrition to improve human health.

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