Immunosuppression - threat

Have our birds become vulnerable to diseases due to a weakened genetic resistance, as many want us to believe, or have other, hidden factors created conditions that makes these an easy target for disease causing organisms?

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Health and disease control remain high priority areas in the management of commercial poultry. Farmers and poultry technical staffs are spending a great deal of time monitoring the health and performance of flocks in production. Various aspects of poultry husbandry impact bird health including environment, genetics, vaccination programs, prophylactic and therapeutic medications, feed additives, nutrition, sanitation and farm biosecurity.

Over the last years, the most important health issue in the international poultry industry is the ban on antibiotics. As a result we can see, particularly in developed countries, a trend to move from treatment to prevention. It is evident that immune system integrity is the key to effectively preventing and dealing with diseases. We must improve the quality of poultry production using the bird's immune system to avoid disease. This can be achieved through properly planned implementation of biosecurity and vaccination. But what are the most common causes of immune system dysfunction?

Immune system

As poultry producers, we are constantly manipulating the immune system and immune response of the birds. Being continually faced with a variety of natural and man-made challenges, overcoming these challenges requires a competent immune response. The avian immune system is complex and involves numerous types of cells and chemical mediators that must act in concert to provide effective response to the challenge. The primary function of the avian immure system is to provide the bird with the ability to resist invasion by, and injurious effects of, infectious disease agents. The system can be broadly categorized as having two parts: innate and acquired.

Innate immunity is the most primitive arm of the immune system and is present and functional as soon as the bird is hatched. Innate immunity can be characterized as non- specific, relatively slow and fairly inefficient. This system, however, is very important and is usually the first line of defence against foreign challenge. The acquired system is composed of numeral and cell-mediated immunity. These types of immune response are also called bursal- derived and thymus- derived immunity, respectively. The acquired immune system is characterized by specificity, heterogeneity and memory. This allows a bird to respond to the second challenge of a particular disease agent with a more rapid and effective immune response.

Humeral immunity is associated with antibodies produced when a bird has been exposed to a particular disease agent. These antibodies are capable of neutralizing, or assisting in the neutralization of specific infectious agents. Antibodies are produced by B- lymphocytes that originate from the bursa of Fabricius. Cell- mediated (cellular) immunity is less easily characterized as it involves numerous different cell types and modes of actions. The T- lymphocytes are the cells associated with this system.

To speak of the innate, humeral and cellular arms of the immune system separately is an oversimplification. All three arms must communicate with each other via chemical messengers to produce a measured and specific response to a foreign invader.

Active immunity

A chicken may become immune to a disease organism by producing antibodies itself or by obtaining antibodies from other animals. When the chicken produces its own antibodies following exposure to foreign material, the process is called active immunity. This occurs after the bird is exposed to a vaccine or a field disease challenge. Active immunity is harmed by anything that damages the cellular or humeral immune systems.

Maternal antibodies

The chick receives pre-made antibodies (maternal) from the hen through the egg. These antibodies are present in the yolk, albumin and fluids of the egg. If the hen has a high antibody titre level to a disease, the chick should also be immune for several weeks.

The flock technical staff must be aware of the maternal antibody level in the chicks to schedule vaccinations. If chickens are vaccinated when maternal antibody titre levels are elevated, the vaccine may be buffered excessively resulting in a reduced response.

The quality of poultry production can be improved by properly

Modern genetics

Modern genetics has much to do with how the birds would develop their im-

to bird health and welfare

managing the bird's immune system to avoid diseases.

mune system. We are well aware of this and there is much field data and reports indicating that advanced genetic selection has improved the economic performance parameters. But the development of immunity has been reduced and poultry producers that have been in this business during the last few decades could tell us that birds were much more resistant before than today.

Sensitive indicator

The avian immune system is both structurally and functionally unique. It is directly influenced by physiological, genetic, nutritional and environmental factors. Therefore, the immune system can serve as a sensitive indicator of management production impacts on poultry health. Based on current developments in genetics, nutrition and biotechnology, the immune system is an ideal candidate for multidisciplinary efforts in improving poultry health.

Immunosuppression

Over the past years, research on immunosuppressive diseases has accelerated. Clearly human HIV infection has driven this subject. Yet, veterinary medicine has long been aware of the detrimental clinical effects of the compromised immune system. In intensive modern production, immunosuppressive agents have been and remain of significant economic concern (vaccination failure, increased mortality and condemnation, poor feed conversion, increased rate of opportunistic infection, increased morbidity and medication costs, etc). Immunosuppression (IS) has been defined as "a state of temporary or permanent dysfunction of the immune response resulting from damage to the immune system and leading to increased susceptibility to diseases".

Numerous immunosuppressive agents affect poultry including viruses, bacteria, parasites, microbial toxins, mycotoxins, chemicals, drugs, nutritional deficiencies and various physical/environmental stressors. Most commonly known IS-viruses are: Infectious Bursal Disease (IBDV), Chicken Infectious Anaemia (CIA), Marek's Disease (MD), Avian Leukosis – J Strain, Reticuloendotheliosis (REV), Hemorrhagic Enteritis Virus (HEV), Reovirus and Adenoviruses as well as Cryptosporidium (*see Box*)

It is possible that more than one immunosupprive agent occurs concurrently in poultry.

It is worth mentioning that the immune response is highly regulated. Breakdown of the regulatory control results in IS. It seems that an immunosuppressive agent must affect several systems or pathways of this regulatory control.

Detrimental combinations

Infection with IBDV was reported to affect the course of a variety of viral, bacterial and protozoa diseases of chickens. The effect of the infection on antibody response to Newcastle Disease was one of the earliest observed IS of the infection. Research has suggested that chickens infected with IBDV exhibit a poor antibody response against IBV in various ways.

In further studies, it was demonstrated that chicks infected early in life with IBDV have increased susceptibility to a variety of viral diseases including IBH, MD, IB, ILT, CIA and reoviruses. Infection was also reported to increase susceptibility to salmonella typhimurium, E. coli, staphylococcus aureus and coccidial infections.

Research has shown that periods of IS will allow the MD virus to come out of dormancy and cause active disease. Evidence has revealed that there is a correlation in which flocks that experience MD are often flocks that also had inadequate IBD protection. In many cases, simply improving the IBD control program has solved persistent MD problems. MD – induced IS has also been associated with a number of outbreaks of diseases such as coccidiosis and even encephalomyelitis.

While CIA can act as immunosuppressant, its association with other immunosuppressive agents can make CIA infections increasingly severe. Examples of combined infections are:

1 CIA suppresses vicinal immunity to turkey herpes virus and produces an early mortality pattern similar to VVMD.
2 Infection with IBD, REV and adenovirus increases the susceptibility of chicks to pathogenic effects of CIA and may enhance the effects of most respiratory pathogens of chickens including NDV, IBV and avian pneumovirus.

Dual infection of 3-week-old chicks with
3 CIA and IBD has a suppressive effect of HVT (Herpes virus of turkey) vaccination immunity.
4 CIA infected chicks have diminished resistance when vaccinated against NDV or ILT.

Susceptibility to E.coli has been shown to be augmented by IBDV, pathogenic reovirus, or adenovirus infection prior to exposure to E. coli and also by MD. Flocks infected with both IBDV and adenovirus may develop severe E.coli – associated respiratory disease in chickens. In many instances, gangrenous dermatitis (GD) is believed to occur as sequel to disease produced by other infectious agents such as IBDV, CIA, REV, IBH. Both GD and IBH occur as squeal to IBD. Lack of antibody to IBD virus in broiler breeders is in correlation with increased susceptibility of their progeny to dermatitis. Another condition predisposing chickens to GD is blue wing disease (BWD). Numerous avian reoviruses and CIA virus have been isolated from chickens affected with BWD. A compromised immune system is the underlying predisposing factor allowing GD to occur.

Mycotoxins

Today, it is estimated that as much as 25% of the world's cereals are contaminated with known mycotoxins, while higher percentages could be contaminated with toxins as yet unidentified. No region of the world escapes these silent killers and their negative impacts on animal productivity and human health are enormous.

It is now realized that the presence of low levels of mycotoxins in the poultry feed may result in poor performance, impaired immunity, decreased resistance to infectious diseases and to tumour development. Several studies have shown that the immunosuppressive effects of mycotoxins are caused by a mechanism resulting from protein synthesis inhibition.

The broad immunosuppressive effects of aflatoxin B1 appears to be directly related to impaired protein synthesis. This process impairs the integrity and efficacy of the network of the immune system. In chickens, aflatoxins reportedly increase susceptibility to cecal coccidiosis, MD, Salmonellas and IBDV.

Immunity acquired through vaccination is also impaired by mycotoxins. For example, aflatoxin B1 ingestion by chickens and, or turkey affects vaccine efficacy for fowl cholera, MD and IB. In vaccinated birds, the occurrence of MD lesions is more severe in the birds fed with aflatoxin B1-mixed feed than in those given control feed. The presence of low levels of mycotoxins in the feed can lead to disease occurrence or relapses even in properly vaccinated flocks. From a public health perspective, increased infectious diseases in food animals including poultry may result in increased animal – to – human transmission of drug resistant pathogens and/or increased antibiotic concentration in meat, milk, and eggs, as a consequence of animal treatment.

The combination of environmental and disease stresses increases the needs for essential nutrients.

Nutrition

Each day, we are learning much about the role of nutrition in the immune responses. Evidence suggests that most nutrients are involved in the development of immune response in poultry. The effectiveness of the immune system is greatly dependent on dietary conditions, being adversely affected by an inadequate supply of nutrients. The combination of environmental and disease stresses increases the needs for essential nutrients. Since we obviously grow birds under field conditions, we should consider the nutritional needs for the development of immune response and disease prevention, in addition to requirements for growth and egg production. Generally, two types of interaction occur between nutrition and immunity. First, nutrition can impact the immune competence of birds and then, their resistance to infectious diseases.

Second, immune responses due to infectious challenges impact growth, reproduction, metabolism and nutrient requirements.

Considerable research has shown that severe, chronic deficiencies of most nutrients impair the immune response and increase susceptibility to infectious disease. Severe nutrient deficiencies are particularly deleterious to the immune system when they occur early life. In this period, the primary lymphoid organs and the maturation of the immune system are developing.

In general, chronically severe deficiencies of micronutrients are more debilitating to the development of the immune system than macronutrients such as energy and protein.

Nutrient deficiencies then are especially damaging to the immune system include linoleic acid, vitamin A, iron, selenium and several of the vitamins.

It has been known for many years, for example, that chicks hatched from vitamin A deficient hens are more suscepti-

Infectious bursal disease (IBD)

IBD is an acute and highly contagious viral infection of chickens. IBD is probably the most important chicken disease that has emerged in the last 30 years. IBD is characterized by the destruction of lymphocytes in the bursa of Fabricius and to a lesser extent in other lymphoid organs. The disease is a major problem in concentrated poultry production areas throughout the world. The majority of field infections are sub-clinical and this form is a more economically important form of the disease.

A sub-clinical form of IBD occurs in chickens less than 3 weeks of age. Chickens present no clinical signs of disease, but experience permanent and severe IS. This IS is due to impairment of the humeral and local immune responses. The cell-mediated immunity is also compromised to a lesser extent and for a short period.

Immunosuppressed chickens have reduced antibody response to vaccinations, strong post vaccinal reactions, increased susceptibility to concurrent or secondary infections especially in the respiratory tract, poor body weights and feed conversion, high mortality and a high rate of condemnation at processing.

In broilers and commercial layers, susceptible chicks exposed to virulent IBD virus within the first week will undergo IS and poor performance and may be refractory to vaccination against NDV and IBV.

Broiler flocks comprising a high proportion of immunosuppressed chicks generally show higher mortality from adenoviral infection and E.coli septicemia. In the presence of TRT virus, swollen head syndrome (SHS) in broilers will be more severe in flocks exposed to IBD.

In parent stocks, early exposure to IBD virus results in severe damage to the immune system. These flocks may show gangrenous dermatitis, necrotic enteritis or coccidiosis during the rearing period.
Immunosuppressed flocks show sub-optimal response to live attenuated priming vaccines against respiratory diseases such as NDV and IBV.

IBDV infection may lead to more severe *E. coil* infections. It has been shown that in flocks with an increasing incidence of E.coli septicemia, affected birds invariably show atrophy of the bursa of Fabricius denoting previous exposure to IBD virus. In contrast, unaffected birds in the flock usually show bursal morphology consistent with age.

IBDV infection is capable of expanding the spectrum of tissues infected by Mycoplasma gallisepticum. For example, mixed infections of MG + IBDV may enable Mg to infect synovial spaces and membranes in the joints, which does not normally occur with ordinary strains of Mg.

Chicken infectious anaemia (CIA)

CIA virus has worldwide distribution and is common in intensive poultry raising areas as evidenced by serology and isolation. In recent years, there has been much discussion on the significance of CIA. Concerns have centred on this disease effects on chickens' immune system and its relationship to other poultry diseases. CIA opens the door for a long list of avian pathogens.

Several studies have shown that CIA results in IS. Susceptible chicks have diminished humeral and cellular immune response and reduced ability to respond effectively to vaccination. The vertical transmission route has been associated with more severe IS.

The extent of economic loss (mortality, decreased production and secondary infection due to IS) that will occur in infected flock depends on the age at which the chickens are infected, the level of their maternal antibody protection against CIA and whether they are concurrently infected with other immunosuppressive viruses such as IBVD or Marek's disease. Co-infection of CIA with these viruses increases the severity of disease due to the CIA.

Research work in the U.K has shown that sub-clinical CIA in broilers has a substantial effect on both performance and profitability. They found that broilers had poor feed conversion ratios increased by 2%, average slaughter weight reduced by 2.5% and overall net income per 1,000 birds reduced by 13%.

Marek's Disease (MD)

MD remains one of the most serious diseases causing economic loss in the poultry industry. It is widespread in virtually all commercial chicken producing areas in

ble to ND virus infection.
Experiments have shown that protein or amino acid deficiency may reduce circulating antibodies to challenge organisms. Feed mineral levels can influence a bird's response to antigen challenge.
Deficiencies of sodium or chloride have been associated with reduced humoral immunity in broilers. Vitamin E and selenium deficient chicks have impaired development of the bursa, spleen and thymus. Trials with birds have indicated that deficient levels of zinc (Zn) may reduce the immune responses.

Management practices

Stress is probably one of the most common causes of IS in poultry. Stressful management-induced immunosuppression is a topic of economic, social and scientific importance. In the poultry industry it is believed that negative economic impact of disease is enhanced in stressed poultry. Under commercial conditions, the chicken is exposed to a variety of stressors that may adversely influence the immune system. Short-term stressors shut available nutrients towards resistance to challenges from bacteria, parasites and toxins and leave the bird susceptible to viral challenge. Chronic (long-term) stressors leave birds more susceptible to infectious agents challenge.

Managerial factors including ventilation, bird density, litter condition, stress levels, days farms are empty or cleaned between flocks, etc may negatively impact effectiveness of the bird's immune system and contribute to an increased challenge in the farm. For example, overcrowding can lead to scratching and picking, which can disrupt the skin barriers and lead to invasion. Every time we take blood samples or administer injections (vaccines, drugs) to birds, we disrupt this barrier and if your equipment is not sterile, we can actually inoculate the invader into the bird.

Variations in energy intake, which may affect immuno-competence, usually result from management practices rather than diet formulation. Feed restriction for broiler breeders and withholding feed in forced moulting practices may affect immune
responses.

We constantly talk about air quality and its effects. What is rarely considered is the effect of poor ventilation on immunity. When birds are forced to breathe poor quality air high in ammonia and dust, the defence barriers of the respiratory tract break down.

Because of this, the bird is not able to effectively eliminate foreign challenge because the system is overwhelmed.

Vaccination itself is also a stress. Further stress during vaccination may reduce the chicken's ability to immune response. Stress management practices play an important role in vaccine failures.

There is no substitute for good management. Vaccines should be used as part of a good management program, not as a replacement. It is obvious that if there were a vaccine that could be administered to alleviate poor management practices, it would be a top selling vaccine.

Biosecurity

Failure to implement a good biosecurity program is the main cause of IS. Biosecurity is a reality and is not just a nice word to be used in poultry disease reference manuals. IS is seen quite often in many poultry operations but not recognized, and in a majority of the cases, the exact cause is not clearly known.

We know by now that if a biosecurity program is in place and the birds have been immunized for the common prevalent diseases in the region, the chances of developing IS are minimal.

A long way to go

Many considerations on biosecurity, vaccination programs, vaccines and other important factors for the control of immunosuppressive agents are available in cited publications. If an immunosuppressive condition is suspected, the problem must be attacked from different directions, by utilizing a solid and systematic investigation program. Through this system the problem can quickly be corrected and leave no room for further deterioration of the immune system.

Evidence shows that there are still many things to learn as well as a long way to go to entirely understand immunosuppressive conditions. ■

the world. This is despite the fact that we have recognized it many years ago and have a large body of research about the disease. This ubiquitous infection is universally ignored as a cause of IS. Research has shown that MD causes depressed cellular and humeral immune responses and subsequent outbreaks of other avian pathogens. For example, MDV infection can increase susceptibility to primary and secondary infection with coccidia. Frequent association of MDV infection with femoral head necrosis, severe respiratory disease and poor physical performance in broiler farms has been demonstrated.

Avian leukosis – J Strain

This vertically transmitted infection emerged among the world's primary breeders during the early 1990's. The condition is usually observed in parent flocks and is characterized by ascending mortality that can attain 20% to 40% of both males and females. ALV-J is not immunosuppressive under controlled laboratory conditions. In the field however, interaction may occur between this virus and CIA.

ALV–J is more frequent in birds where control of MDV has failed due to early exposure to field challenge and/or challenge with highly virulent pathotypes of MDV. Other immunosuppressive agents including IBD, CIA, reovirus, reticuloendotheliosis and mycotoxins can compromise the bird's ability to mount adequate immune response in the face of ALV–J challenge leading to higher tumour incidence and poor performance.

Reticuloendotheliosis (REV)

Humeral and cellular immune responses are frequently depressed in chickens infected with REV strains. Indeed, IS may be the most economically important consequence of infection with REV depressed antibody responses to MDV, turkey herpes virus (HEV) and NDV are documented.

Research has shown that infection with REV may make chickens more susceptible to reactions from ILT vaccine, to natural fowl pox infection, IBV, to mortality induced by Eimeria tenella and salmonella typhimurium and may have been more susceptible to necrotic dermatitis.

Hemorrhagic enteritis virus (HEV)

HE is an economically important disease of turkey and pheasants. HE virus is ubiquitous and commercially raised turkeys acquire the virus from the environment. HE causes IS.
A turkey flock undergoing HEV – induced IS may experience an increased incidence of infections such as colibacillosis and rhinotracheitis. It has been shown that HEV alone or in combination with other agents including Bordetella avium, NDV and Mycoplasma meleagridis (MM) predisposes turkey to secondary infection with E. coli in the field.

Reovirus

Reoviruses are hardy viruses found in healthy as well as sick birds. They are best known as the cause of infectious tenosynovitis in chickens and turkeys. It seems that some selected reovirus isolates have potential to cause some degree of IS. Reoviruses may exacerbate disease conditions caused by other pathogens including CIA, E. coli and NDV.

Adenoviruses

As with reoviruses, adenoviruses can be found in healthy as well as sick birds. In the past, most outbreaks of inclusion body hepatitis (IBH) were believed to result from adenovirus infection of birds whose immune system was compromised due to IBDV or CIA infection.
While adenoviruses are not considered sever immunosuppressant, they are opportunistic in nature and can cause some detrimental problems with immunosuppressed birds. There is no doubt that infections with IBDV and/ or CIA are important players in the severity of many adenovirus infections.

Cryptosporidium

Cryptosporidium is frequently found in the respiratory tract of turkeys (less commonly in chickens). It has been suggested that it may enhance respiratory diseases caused by avian pathogens (e.g. E. coli), particularly when birds are exposed to virulent IBDV. ■