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Clinical Aspects of Immunosuppression in Poultry

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SUMMARY. Chickens, turkeys, and other poultry in a production environment can be exposed to stressors and infectious diseases that impair innate and acquired immunity, erode general health and welfare, and diminish genetic and nutritional potential for efficient production. Innate immunity can be affected by stressful physiologic events related to hatching and to environmental factors during the first week of life. Exposure to environmental ammonia, foodborne mycotoxins, and suboptimal nutrition can diminish innate immunity. Infectious bursal disease (IBD), chicken infectious anemia (CIA), and Marek’s disease (MD) are major infectious diseases that increase susceptibility to viral, bacterial, and parasitic diseases and interfere with acquired vaccinal immunity. A shared feature is lymphocytolytic infection capable of suppressing both humoral and cell-mediated immune functions. Enteric viral infections can be accompanied by atrophic and depleted lymphoid organs, but the immunosuppressive features are modestly characterized. Some reoviruses cause atrophy of lymphoid organs and replicate in blood monocytes. Enteric parvoviruses of chickens and turkeys merit further study for immunosuppression. Hemorrhagic enteritis of turkeys has immunosuppressive features similar to IBD. Other virulent fowl adenoviruses have immunosuppressive capabilities. Newcastle disease can damage lymphoid tissues and macrophages. Avian pneumovirus infections impair the mucociliary functions of the upper respiratory tract and augment deeper bacterial infections. Recognition of immunosuppression involves detection of specific diseases using diagnostic tests such as serology, etiologic agent detection, and pathology. Broader measurements of immunosuppression by combined noninfectious and infectious causes have not found general application. Microarray technology to detect genetic expression of immunologic mediators and receptors offers potential advances but is currently at the developmental state. Control methods for immunosuppressive diseases rely largely on minimizing stress, reducing exposure to infectious agents through biosecurity, and increasing host resistance to infectious immunosuppressive diseases by vaccination. A longer term approach involves genetic selection for resistance to immunosuppressive diseases, which has shown promising results for MD but equivocal results for IBD and CIA.

Key words: immunosuppression, chicken, turkey, poultry, infectious bursal disease, chicken infectious anemia, Marek’s disease, ammonia, mycotoxins

Abbreviations: BF = bursa of Fabricius; CAV = chicken anemia virus; CIA = chicken infectious anemia; FAV = fowl adenovirus; HE = hemorrhagic enteritis; HEV = hemorrhagic enteritis virus; HVT = turkey herpesvirus; IBD = infectious bursal disease; IBDV = infectious bursal disease virus; IBV = infectious bronchitis virus; MD = Marek’s disease; MDV = Marek’s disease

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Immunosuppression in poultry

Production environments for chickens, turkeys, and other poultry result in exposure to immunosuppressive stressors and infectious diseases. An understanding of the presence and pathogenesis of immunosuppressive risk factors is essential to successful management for optimal health and welfare and realizing the full contributions of genetic and nutritional advancements for efficient production. The purpose of this review is to merge research findings with clinical and diagnostic observations on the causes and pathogenesis of immunosuppression in the production of poultry.

STRESSORS SUPPRESSING INNATE IMMUNITY

Incubation, hatching, and the posthatch period. Adjustments of incubation and hatching conditions generally lag genetic advances in rate of gain and change in carcass composition such as increased pectoral muscle mass in high-yield broilers. This creates a challenge to obtain maximal hatchability in the shortest hatch duration; difficult or extended hatching times impose multiple stresses. The high-yielding broiler of today is sensitive to the incubation and hatching environment, while at the same time, it is challenged to mount an immune response to vaccines administered in ovo and in the immediate posthatch period. Suboptimal incubation can result in a variable population of chicks with stresses related to body temperature, ventilation, and hydration. A difficult hatch can deplete total body energy and add to the nutritional stress that may be experienced during the first week of age, and beyond (Fig. 1). Incubation and hatching stresses are actually modeled by dexamethasone injection, which induces lymphocyte cellular death by apoptosis.

Chick handling, extended transportation times from hatchery to farm, extended time to first feed intake, and suboptimal brooding may impose additional physiologic stresses. Stresses such as ammonia, heat, and electrical shock (as might be experienced as stray voltage), increase the circulating heterophil percentage and decrease the lymphocyte percentage (heterophil:lymphocyte ratio) in an additive manner. The blood leukocyte changes are a more reliable indicator of stress than the concentration of plasma corticosterone.

In commercial egg-type layers, physiologic stress associated with the onset of egg production and the social stress of new penmates and new housing increase susceptibility to colibacillosis just after the move to the layer house (E. Gingerich, personal comm., 2009). Colibacillosis in older birds is associated with the stress of pecking and scratching trauma related to age-related feather loss.

Housing environment. Ammonia is an irritant gas produced by microflora of the cecum from uric acid and amino acids present in the lumen, and in poultry environments, by the action of litter microflora on feces. Ammonia concentrations are highest in poultry housing during the coldest months of the year. Ammonia causes photophobia due to conjunctivitis and edema, inflammation, and ulceration of the cornea. Clinical signs and lesions observed with high ammonia concentrations in poultry houses are somewhat more severe than predicted from experimental exposure to ammonia, suggestive of the contributing pathogenic effects of dust, airborne bacteria, and endotoxins, among the other contaminants of air in poultry houses. At physiologic pH, nonionic ammonia concentrations remain low but are primarily responsible for the toxic effects, and present measurement methods do not distinguish ionic from nonionic forms.

Ammonia induces the secretion of mucus from goblet cells, stimulated by the changes in pH of the airway surface fluid and possible contributions from nerve stimulation and inflammatory mediators. Respiratory mucus is composed of mixed secretions, chemically distinct, from different cellular synthesizing sites. Changes in the chemical and physical properties of the mucus occur by selective action on the secretion of one or more of the contributing glycoproteins. This increases the viscoelasticity of the mucus and decreases the efficiency of mucociliary clearance of the respiratory tract. Further impairment is due to ciliosis and loss of cilia, increased production of respiratory mucus, and the accumulation of particulate matter.

Formaldehyde exposure during hatching is an established practice to reduce the level of contamination of hatching eggs at or near the time of transfer to the hatch. The practice has variable application due to occupational safety concerns. Chick embryos exposed to formaldehyde during the last 3 days prior to hatch have been shown to develop excessive accumulation of mucus, matted cilia, loss of cilia, and sloughing of the epithelium in the upper respiratory tract.

Feed and nutrition. Mycotoxins are a diverse group of biotoxins produced as fungal metabolites. Many mycotoxins target components of innate and acquired immunity, contributing to an increased severity of concurrent infectious disease. Aflatoxin is broadly immunosuppressive in chickens, turkeys, and ducks, as shown by increased severity of concurrent diseases, vaccination failures, depletion of lymphoid tissues, impaired functions of lymphocytes, and macrophages, and a reduction in serum complement.

Trichothecenes such as T-2 toxin and diacetoxyscirpenol damage protective barriers of mucosal membranes and feathers. Fumonisins and other toxins produced by Fusarium moniliforme cause lymphoid depletion, reduced antibody formation, and toxicity to macrophages and lymphocyte functions. Trichothecenes cause generalized atrophy of lymphoid organs, impairment of cell-mediated immunity, humoral immunity, vaccination responses, and phagocytic activity; and increased severity of concurrent infections.

Ochratoxins cause generalized atrophy of lymphoid organs, impairment of cell-mediated immunity, humoral immunity, vaccination responses, and phagocytic activity; and increased severity of concurrent infections.

A diverse set of other mycotoxins, including citrinin, cyclopiazonic acid, sterigmatocystin, rubberatoxin, causes generalized lymphocyte depletion and immune dysfunction in various poultry species.

Dietary characteristics can modulate a bird's susceptibility to infectious challenges. Subtle influences due to the level of nutrients...
or the types of ingredients may at times be of critical importance to the immune system (reviewed by Klasing (131)). Adequate nutrition is critical to the development of the immune system in the embryo and the posthatch period during the seeding of lymphoid organs. A reduction in the time that feed is freely available to young broiler chickens results in atrophy of the bursa and thymus (83). The nutritional requirements for normal lymphoid organ development may not be sufficient for the immune responses required by infectious disease challenge. In this situation, nutrients formulated and intended for maintenance and growth are used instead for immune response, inflammation, and repair.

Fatty acids and vitamins A, D, and E have direct regulatory roles on leukocytes and are essential for maintaining an adequate immune response to disease challenges (1,141,142,236). Rancid fats produce free radicals that are broadly damaging to gut epithelium, liver, and lymphoid tissues (168). Vitamin E is protective of free-radical formation and is integral to immunoreactive cellular functions; subclinical deficiencies are insidiously damaging to immune functions.

In commercial egg-type layers, nutritional stress occurs in underweight young hens that are not producing eggs and in older hens on diets of declining nutritional density. These stresses are associated with increased susceptibility to infections by *E. coli* and *Staphylococcus* spp. (E. Gingerich, personal comm., 2009).

**DISEASES SUPPRESSING ACQUIRED IMMUNITY**

**Infectious bursal disease (IBD).** The IBD virus (IBDV, *Birnaviridae*) is horizontally transmitted and infects young chickens. IgM+ (B) lymphocytes in the bursa of Fabricius (BF) are targeted (90), causing rapid necrosis and depletion of lymphocytes from the bursal follicles (232). The BF is principally involved, but lymphoid tissues elsewhere (spleen, cecal tonsil, proventriculus) are also affected. The primary response to IBDV infection occurs as an influx of T lymphocytes (126,127,253). Intrabursal T cells and T cell–mediated responses are important in viral clearance and are necessary in promoting recovery from infection (127). Cytotoxic T lymphocytes (CD4+, CD8+) help to limit viral replication but promote bursal tissue damage and delay tissue recovery, possibly through the release of cytokines and cytotoxic effects (212). In comparisons of the pathogenesis of vaccine strains of IBDV, the magnitude of the T-cell responses in the BF during IBDV infection is influenced more by the virulence of the IBDV than the viral load in the tissue (200). The local T-cell events in the bursa alone may not be indicative of a rapid and protective immune response (213).

Acute infection may occur as clinical or subclinical disease, and mortality is a feature of very virulent strains of IBDV. During acute infections, chickens develop systemic disease and may develop lesions in the lymphoid tissues, liver, and kidney, in association with circulating immune complexes (143,237). Chickens that survive the acute infection clear the viral infection, and bursal follicles are repopulated with IgM+ B lymphocytes (125). As the virulence of the IBDV strain increases, the follicular repopulation or restitution decreases. For individual follicles, two sequelae are observed histologically: large reconstituted follicles with numerous lymphocytes in the cortex and medulla, and small poorly developed follicles with a poorly discernible cortex and medulla (268).
mostly undifferentiated follicles have reduced ability to mount an antibody response, indicating that B cells in these follicles are unable to produce peripheral B cells with an effective immunoglobulin repertoire.

Neonatal chickens that survive the acute infection are immunosuppressed despite repopulation of the bursa with B cells. When IBD occurs in chickens 14 days of age or younger, B lymphocyte seeding of secondary lymphoid centers is curtailed, resulting in a permanently defective humoral immunity, and leaving the chicken susceptible to secondary infections (49,108,183). In chickens older than 14 days, IBD causes transient depression of systemic antibody production and, with necrosis of plasma cells in the Harderian gland, diminished mucosal immunity (48,50,90,99). Cell-mediated immunity and heterophil and macrophage functions are also transiently depressed (48,50,137).

In the decades since the original descriptions, IBD has become ubiquitous in most commercial poultry flocks worldwide. Advances in protecting young chickens from mortality and permanent immunosuppression have been realized through breeder hen immunization for transfer of high levels of maternal antibody, and vaccination of the young chicken with attenuated strains of IBDV (140). IBD today still occurs in broilers, young breeders, and commercial layer pullet replacements, but the window of susceptibility is about 20 to 30 days of age. This is reflective of vaccination programs that provide maternal immunity to progeny, and the effectiveness of attenuated vaccines in providing acquired immunity to IBDV in the chick (257). In this scenario, the severity and duration of the transient immunosuppression are likely keys to the impact of IBD and the effectiveness of IBD vaccination programs. As the response and recovery from acute IBDV infection require intact immune responses, poultry are also vulnerable to other immunosuppressive agents and disease.

Bursal disease is caused by classical stains of serotype 1 IBDV associated with clinical IBD, antigenic variant stains of serotype 1 IBDV associated with subclinical disease, and very virulent pathotypes associated with moderate to high mortality (11,61,177). The subclinical characterization of the antigenic variants is a matter of perspective. In the author’s experience, it is relatively common for broilers between 20 and 30 days of age to have clinical signs of huddling, diarrhea, and mild mortality. At necropsy, the bursa is small, and histologically, there are apoptosis and necrosis of lymphocytes consistent with acute IBD.

IBD interacts with infectious bronchitis by interfering with effective immunization, enabling persistent respiratory infections by infectious bronchitis virus (IBV), and increasing the severity of nephropathogenic bronchitis (68,81,223,257,267). IBD reduces or delays the secretory antibody to IBV in tears, allowing a permissive environment for IBV replication in the Harderian gland and the secretion of infectious virus (72,260).

IBD interacts with Newcastle disease by increasing the severity of Newcastle disease outbreaks (188), interfering with the antibody response to immunization (8,65,78,192,219), reducing the resistance to Newcastle disease virus (NDV) challenge (223), and prolonging the duration of NDV shedding during infection (114).

Under circumstances in which there is early onset of IBD, chickens can have increased risk for Marek’s disease (MD). Exposure to IBD at less than 1 wk of age increases susceptibility to MD (78). Pathogenic bursal disease virus has been shown to transiently decrease the protection of turkey herpesvirus (HVT) vaccine for virulent MD virus (MDV) (230). Bursal disease causes decreased virus-neutralizing antibody to HVT vaccination and reduces antiviral immunity to MDV (110).

In chickens, IBDV infection leads to persistence of reovirus in tissues, and lower antibody response to reovirus compared to reovirus alone (176).

IBD is associated with increased severity of bacterial diseases of chickens, including salmonellosis, colibacillosis, staphylococcosis, and clostridial infections. Bursal disease and severe enteritis were predisposing conditions for a severe outbreak of subcutaneous clostridial infection (gangrenous dermatitis) involving Clostridium perfringens and Clostridium septicum in broilers (96).

Bursal disease increases general susceptibility of Salmonella Typhimurium (ST) and decreases the humoral immune response to ST infection in broilers (13,274). In young layer pullets, IBDV coinfection increased the severity of lesions from Salmonella enterica serovar Enteritidis (SE), increased mortality, and at sexual maturity, increased rate of egg transmission of SE (194).

In most respiratory diseases of poultry, E. coli is the final pathogen to express sequentially, following IBDV and other immunosuppressors, and a primary respiratory disease. IBD can increase the susceptibility to E. coli without a predisposing viral infection (105,171,182). The pathogenesis involves the failure of bacterial clearance from the circulating blood once colisepticemia is established, even by relatively apathogenic strains of E. coli (222).

Chickens with IBD are more susceptible to Staphylococcus aureus (227), which can express as staphylococcal gangrenous dermatitis (26). In young broiler breeders, staphylococcal and coliform-induced chondronecrosis and osteomyelitis are predisposed by ad libitum feeding, resulting in excessive body weight and immunosuppression involving IBD and chicken infectious anemia (CIA) (161,162).

In outbreaks of coccidiosis, IBD and ensuing bursal atrophy are associated with increases in lesion severity and mortality (86,190) and apparent failure of anticoccidial drug treatments (155). Although immunity to coccidia is not blocked, suboptimal immunity can occur. Bursal disease has been associated with increased hemorrhaging during coccidiosis caused by Eimeria tenella (74).

CIA. The chicken anemia virus (CAV, Circoviridae) is vertically transmitted from a hen that is acutely infected during egg production, and it is transmitted to the developing embryo (32,286). When the chick hatches, CAV targets hemocytoblasts in the bone marrow and lymphocytes (CD4+, CD8+) in the thymus, resulting in aplastic anemia, thrombocytopenia, leukopenia, and thymus depletion in chickens 7 to 14 days of age (100,251,252,285). The chicks develop a fatal gangrenous lesion on the wings called blue wing (17,69,79,163). During the acute infection, the virus is shed to penmates through the digestive tract and feather dander (41). Chicks with aplastic anemia are immunosuppressed and susceptible to adenovirus infections and bacterial disease (184,224). The adeno-associated virus reported in the early 1970’s by Yates et al. (275) was likely CAV.

Nearly simultaneous with the isolation and characterization of CAV was recognition by Yuasa et al. (283) of the highly protective role of maternal antibody in preventing aplastic anemia in progeny chicks. They observed that breeder flocks that were seropositive to CAV produced chicks that were refractory to aplastic anemia and demonstrated this in challenge studies. Aplastic anemia and blue wing are now largely controlled by ensuring that hens are exposed to CAV prior to the onset of lay (80,221,262). The hen develops antibody to CAV, which is transferred to and protective of the progeny chick (80,262), even though the hen may continue to shed CAV through the reproductive tract (18). As a result of broad application of this basic control method, blue wing disease is observed less frequently in broiler and layer production today.
From the perspective of poultry production, the prevention of aplastic anemia and blue wing disease in young chickens by CAV vaccination in breeders provided somewhat false assurance that the CAV problem was resolved (80). It was recognized early on that chickens older than 14 days could be infected with CAV. The rapid development of antibody and the lack of clinical signs were suggestive of age-related resistance to aplastic anemia (284,285). Subclinical immunosuppression by CAV in chickens older than 2 wk of age is now recognized as economically important to production (164). With the decline of maternal immunity, chickens become again susceptible to infection by CAV, which is ubiquitous in poultry environments (240,277). In older chickens, the bone marrow is spared, but the thymus is infected by CAV and depleted of lymphocytes by apoptosis (112,117,239,255). The chickens have impaired T lymphocyte and macrophage activities, and lose bactericidal capability (153) for up to 4 wk postinfection. Material immunity can be low in a percentage of chicks during the first week and is typically depleted by 10 to 14 days of age (240) (B. Hopkins, personal comm.; F. J. Hoerr, unpubl. data), but can persist to 20 days of age (256). Depending on the level of exposure, oral intake of CAV as well would occur with natural exposure may require up to 10 to 14 days to induce peak virus load in the thymus, which correlates with the severity of thymus atrophy. Thus, chickens with declining maternal immunity become susceptible to CAV at 20–30 days of age, or perhaps younger if maternal antibody protection is marginal. The thymus depletion is a subclinical event (117), but broilers with CAV-depleted thymuses develop secondary infections, including gangrenous dermatitis, coccidiosis, and viral and bacterial infections of the respiratory tract (86).

The potentially important interaction between IBDV and CAV was recognized by Yuasa et al. (285), who actually had to neutralize IBDV (and reticuloendotheliosis virus [REV]) from their infective material used during the initial characterization studies and serial passage of CAV. Chickens coinfeared with IBDV have increased susceptibility to CAV infection at older ages (282), are more susceptible to contact infection by CAV, have higher mortality rates (224), and have prolonged acute phase prior to recovery or mortality (36). In chickens 35–40 days of age, IBDV infection enhances CAV infection by inhibiting virus-neutralizing antibody to CAV, which prolongs CAV viremia, and there is increased presence of CAV in the distal intestine (106). In broilers, IBDV infection delays the recovery of the thymus from CAV-induced lymphocyte depletion (256). Although bursal atrophy is a feature of CAV infection, the pathogenesis does not involve CAV replication in the bursa (2). In broiler production, the onset of bursal atrophy and thymus atrophy, consistent with bursal disease and CIA, respectively, is suggestive of these two diseases being sequential or concurrent subclinical immunosuppressive risk factors underlying the presenting clinical diseases (86,257).

The pathogenesis of MD can be enhanced or inhibited by CAV, depending on the titer of the challenge dose of MDV (111).

Early CAV infection resulted in decreased protection from vaccination for either Newcastle disease or laryngotracheitis, and combined CAV and IBDV challenge also reduced vaccine protection from fowl pox (37). CAV-infected chickens had more severe respiratory reaction to attenuated NDV vaccine, with reduction in growth (44).

In broiler flocks in Alabama, peak isolation of cycling vaccine strains of IBV coincides with the onset of bursal atrophy attributable to IBDV infection at 20–30 days of age, and thymus atrophy attributable to subclinical CAV infection that emerges at 30–40 days of age (92,257). Experimental evaluation of the immunodeficiency created by coinfection with CAV and IBDV on the outcome of IBV infection revealed that clinical signs and histologic lesions were more persistent in immunodeficient chickens. At the same time, IBV RNA concentrations in tracheas and lachrymal fluids were higher and more persistent in immunodeficient chickens. Coinfection with CAV and IBDV reduced B cells and T helper cells in the Harderian glands and cecal tonsils in response to IBV, and slowed the kinetics and/or reduced the magnitude of the mucosal immune response against IBV (260).

CAV infection is a risk factor for bacterial infections, due to reduced bactericidal capabilities of macrophages from infection by CAV that can last for up to 28 days (153,154). CAV is associated with staphylococcal infections (69,161) and gangrenous dermatitis (16,86,202,224). Respiratory infections typically involve E. coli infections as the chief cause of mortality and losses at processing. Increased medication costs linked to bacterial infections are one factor in the association of CAV with decreased performance and profitability of broilers (158,164).

MD. MD causes immunosuppression and lymphoma formation in chickens. The history of MD vaccination reflects the ongoing emergence of virulent strains of Marek's disease virus (MDV) capable of breaking through protection of once-effective vaccines. Infection by MDV causes lymphotoxicotic infection and atrophy of the BF and thymus (23), lymphopenia, and reduced humoral immune response (62,107,132). The degree of immunosuppression is a criterion of virulence of emerging strains (269). Vaccines that protect against lymphoma formation by virulent MDV have a sparing effect on immunosuppression but may not provide complete protection (107,214). Despite the immunosuppressive potential of MDV, detection of MD-induced immunosuppression is a diagnostic challenge, given the ubiquitous nature of IBDV and CAV. An indirect but practical approach to this is that immunosuppression by MD should be expected to accompany emerging problems with MD lymphomas, skin tumors, or other MD syndromes.

Interactions of MD with IBD and CIA are described in the preceding respective sections.

Retroviral tumor diseases. Avian leukosis of chickens and reticuloendotheliosis of turkeys, chickens, and other avian species cause tumors, reduced productivity, immunosuppression, and other production problems in affected flocks (64). In chickens, replication competent REV strain A and chicken syncytial virus have been shown to cause a runting syndrome and bursal atrophy (67). Chicks with tolerant infections by REV become immunodepressed (270), which may contribute to the development of acute leukemia by inhibiting the proliferation of cytotoxic cells directed against the tumor cell antigens (15,265). Chicks infected with REV and challenged with NDV developed more severe clinical signs and had reduced antibody response and prolonged recovery time (280). A myeloblastosis strain of avian leukemia virus capable of inducing osteopetrosis caused atrophy of lymphoid organs and decreased macrophage function and bacterial clearance (38,39,238). An erythroid blastosis strain of ALV caused thymus atrophy and decreased T-cell competencies (210).

Hemorrhagic enteritis (HE) of turkeys and other adenovirus infections. The adenovirus that causes HE of turkeys (HEV, type II avian adenovirus) causes acute cytopathic infection of IgM+ lymphocytes (B cells) and macrophages (247). The infection suppresses B lymphocyte and macrophage functions, leaving pouls 6 to 11 wk of age susceptible to E. coli infections (167). The acute clinical disease is an immune-mediated (T lymphocyte) HE of the proximal small intestine (248), for which the pathogenesis involves proinflammatory cytokines (211). The acute phase also is
characterized by splenomegaly (231), with virus replicating primarily in the spleen and cecal tonsils. Active infections are indicated by large intranuclear inclusion bodies in reticuloendothelial cells and in renal tubular epithelium (167). Acute HE exacerbates *E. coli* infections in the immunosuppressed poult (242) and initiates seroconversion to HEV (167). An *E. coli* septicemia syndrome involving synovitis, osteomyelitis, and hepatitis with green discoloration of the liver is a sequela to HE infection in 8- to 11-wk-old turkeys (52).

Although they are caused by different viruses, HE in turkeys has immunosuppressive effects similar to IBD in chickens (225). Both viruses target IgM+ lymphocytes (B cells) and macrophages, and the acute stage of the disease is followed by immunosuppression and increased susceptibility to infectious disease. Virulent HEV and avirulent vaccine strains can predispose turkeys to bacterial infection (185,197,258). HE reduced the response to vaccination of turkeys against Newcastle disease (181).

Virulent strains of fowl adenovirus (FAV) capable of outbreaks of inclusion-body hepatitis in the absence of immunosuppression by IBD or CIA have marked tropism for lymphoid tissues. Atrophy of the bursa, thymus, and spleen occurred with challenge studies involving FAV serotypes 1, 4, and 8 (228,234) and an isolate not further typed (178). These virulent FAVs have viral tropism for lymphocytes and cause impairment of humoral and cellular immune competencies. The severity was augmented by aflatoxin (233). Multiple avian adenovirus strains can increase susceptibility to *E. coli* infection in chickens (46,222).

**Enzootic viral diseases.** Viral enzootic syndromes in chickens and turkeys (running stunting syndrome [RSS]; poultry enzootics and mortality syndrome [PEMS]) involve one or more etiologic viruses, and contributing management issues such as short down time between flocks. Astrovirus, rotavirus, reovirus, parvovirus, and others have been identified in young broilers (7–14 days) and young turkeys with diarrhea and growth reduction. In the author's experience, broilers with RSS commonly show atrophy of the BF and thymus at necropsy, and histologically mild to moderate lymphocyte depletion. Similar lesions have been reported for RSS cases in broilers in Australia (215) and Mississippi (173), and in turkeys in Ireland (160). The pathogenesis is not known. In the United States, chicks with acute RSS typically consume litter and the lesser mealworm *Alphitobius diaperinus* (Panzer). This interference with normal feeding behavior and interrupted nutrition could contribute to atrophy of lymphoid tissues (83). In some cases, histologic examination of liver shows bile duct proliferation in one or more chicks per case, suggestive of contributions to immunosuppression by hepatotoxicity from natural toxins.

Lymphocyte depletion in the lymphoid tissues occurs in turkeys with PEMS (207). Turkey enteric coronavirus is associated with PEMS (24), and turkeys inoculated with coronavirus and *E. coli* developed lymphocyte necrosis and depletion in the BF (85). Thymus atrophy is a lesion also associated with PEMS, and it occurs in turkeys inoculated with astrovirus (14,133,229). A small round virus, possibly an enterovirus or astrovirus, can replicate in lymphoid tissues of turkeys, causing lymphocyte necrosis and depletion of lymphoid organs, and corresponding reductions in lymphocytes subpopulations in circulating blood (207,226,249,281).

Virulent strains of avian reovirus cause atrophy of lymphoid tissues and interfere with humoral immunity (43,174,175,217,241). Reoviruses can replicate in monocytes but not in lymphocytes (170); thus, the lymphoid atrophy is not caused by reovirus tropism specifically for lymphocytes, in contrast to IBDV, CAV, MDV, and some of the other enteric viruses.

Goose parvovirus is the etiology of a fatal hepatitis in young geese (Derzsy's disease) (20). A parvovirus related to but distinct from goose parvovirus causes degenerative rhabdomyopathy in Muscovy ducklings (201,271). Chickens and turkeys can be infected by paroviruses, which may have a role in naturally occurring enteric infections (45,288). A chicken parvovirus has been shown to be vertically transmitted, and hatched broiler chicks had growth retardation, feather dysplasia, and bone disorders (128,129,130).

Some mammalian paroviruses have the potential to be immunosuppressive, or exert their pathologic effects in immunosuppressed hosts (7,159,216). There is some confusion in the literature about CAV and a parvovirus-like virus (80), possibly due to the fact that both are small viruses not readily differentiated by morphology in clinical specimens.

**Respiratory viruses.** Newcastle disease causes lymphocyte necrosis and depletion from lymphoid organs (4,33), and it causes apoptosis of peripheral blood lymphocytes and mononuclear cells (136,138), which may increase susceptibility to secondary bacterial infection.

Cases of pneumovirus infections in turkeys are characterized by concurrent bacterial and viral coinfections. Pneumovirus replicates and causes cytopathology in the upper respiratory epithelial cells (25), causing impairment of protective clearance mechanisms. The mechanism of immunosuppression appears to involve innate respiratory immunity more than acquired immunity. Pneumovirus infection augments bacterial infection of the lung and air sacs, and with more invasive bacterial infection, there is deeper (bronchial) infection by the pneumovirus (150). Avian pneumovirus infections render turkeys more susceptible to infections by *E. coli*, *Ornithobacterium rhinotraceale* (ORT), and Bordetella avium (113,148); exacerbate infections by *Chlamyaphila psittaci* (147); increase the severity to avian paramyxovirus challenge (151); and decrease the efficacy of HE vaccine (30). Chickens with pneumovirus infections become more susceptible to *E. coli* (5,150) and ORT (259). This can manifest as swollen head syndrome with rhinitis, sinusitis, facial cellulitis and edema, and inflammation of the cranial air spaces (150).

**Other potentially immunosuppressive diseases and agents.** *E. coli* infections alone can induce marked lymphocyte depletion from the bursa and thymus in chickens (182). Infection of turkeys by eastern equine encephalomyelitis and Highlands J. viruses causes lymphocyte necrosis and depletion from lymphoid tissues (66).

**Measurements of immunosuppression.**

For the poultry diagnostician, detection of immunosuppression largely focuses on detecting specific diseases by serologic surveillance, isolation, or molecular detection of the etiologic agent, or presumptive lesions identified at necropsy or by histopathology. Assays to assess immunocompetency are largely used in the research laboratory; however, a broader approach could assess combined environmental and infectious contributions of immunosuppression (47).

The heterophil:lymphocyte ratio in the circulating blood is a general indicator of stress and may provide general assessment of immunocompetency (91). Measurements of chicken interferon-alpha and interferon-gamma mRNA have been proposed as a general assessment of immune function. Both are increased by subclinical infections by either IBDV or CAV (209), and could be assessed following a brief laboratory challenge by inactivated Newcastle virus (187). Interleukin-2 has been proposed as a general measure of cell-mediated competency in the chicken intestine (40). Whole-blood
lymphocyte stimulation assay is a relatively simple assay of circulating T-cell responses and has application for the evaluation of coccidiosis outbreaks and of vaccine efficacy (250). Functional assessment of peripheral blood monocytes has been proposed to assess immune function of cattle, including ingestion of \textit{Staphylococcus aureus}, antibody-dependent cell-mediated cytotoxicity, and chemiluminescent assays (245). While these proposals have existed for some time, none has seen consistent application or gained common acceptance.

A functional genomics approach to the study of avian innate immunity uses cDNA microarray, which is capable of testing for over 4000 genes (121). The avian innate immunity microarray contains 25 avian interleukin, chemokine, and cytokine elements. The array also contains elements for several innate immune pathways, including genes involved in the Toll-like receptor pathway, avian interferon/antiviral response pathway genes, and genes involved in apoptosis, antigen presentation, and the oxidative burst. The avian specific microarray can test for global gene expression patterns in a number of immunologically relevant tissues and in chickens, turkeys, and ducks. The array has also been evaluated for its ability to monitor the avian immune response to both bacterial (avian pathogenic \textit{E. coli}) and viral (avian influenza) avian pathogens.

Analysis of cytokine and chemokine gene expression following coccidiosis revealed that the primary response to coccidiosis is robust in immunocompetent chickens (97,98). This procedure holds the potential for characterizing specific immune response deficiencies occurring as a result of some of the immunosuppressive conditions described herein.

\textbf{CONTROL OF IMMUNOSUPPRESSION}

The control of immunosuppressive diseases depends on biosecurity to prevent exposure to the causes of immunosuppressive diseases, and increasing the resistance to challenge from immunosuppressive agents through immunization and genetic selection. Today, with ever-expanding flock sizes and increasing farm size, litter is reused due to economic and environmental constraints, cleaning and disinfection become seasonal events rather than occurring after each flock, and there is variable application of all-in, all-out management. These factors all contribute to an environment where challenge from ubiquitous immunosuppressive agents is virtually certain. MD, IBD, and CIA are not unique to these environments, but they are a constant challenge due to the ability of many animals to replicate and shed large quantities of virus.

Immunosuppression has historically cost the poultry industry in increased mortality and in performance factors during rearing, and it has negatively impacted the processing of chickens due to associated health problems. Strategies to control immunosuppression in broilers and commercial layers are largely based on vaccination programs for breeders and broiler progeny, and management to minimize stress during rearing (70).

The genes of the major histocompatibility complex (MHC) encode proteins that are essential in the functioning of the immune system. The MHC antigens of chickens are cell-surface glycoproteins of three different classes: class I (B-F), class II (B-L), and class IV (B-G), which are essential in the regulation of cell–cell interactions (139). A second histocompatibility complex of genes occurs in the chicken, Rpp-Y, composed of MHC class I and class II genes (264). Immunogenetic selection for specific resistance to immunosuppressive infectious diseases has yielded variable results. Strong association of genes for resistance to MD (19,146,198,264) has resulted in the greatest application to genetic selection. Selection for specific immunogenetic traits is a challenge because selection for disease resistance must be balanced with desired production traits (88,287). Immunogenetic associations for resistance to IBD are equivocal (21,101,116), but differences occurred in the antibody response of various MHC haplotypes to IBDV infection (63) and to inactivated IBDV vaccine (115). CAV infects cells bearing class II antigens in the bone marrow and T-helper lymphocytes in the thymus (3). An MHC effect on resistance to CAV infection was not detected (114), but induced mutations on CAV had an effect on virus replication, cytopathogenicity, and down regulation of MCH class I genes in infected cells (193).

Immunogenetic control of general antibody responsiveness is complex with multiple loci of MHC genes involved (279). As an example of the complexity of these associations, the selection of chickens as high-antibody responders had no effect on genetic resistance to \textit{E. coli} infection (54) or \textit{Eimeria tenella} coccidiosis (53). The MHC has been primarily identified with genetic control of immune response and disease resistance, but lesser characterized genes outside of the MHC also regulate immunoresponsiveness (139). The existence of Toll-like receptors in chickens and turkeys provides a genetic basis for selection for enhanced innate immunity (89,276). Understanding the interaction of adjuvants with immunogenetics may lead to improved vaccines (278).

\textbf{PERSPECTIVE}

With current MD vaccines keeping MD under control, IBD and CIA are currently the two major immunosuppressive diseases in broiler production. The two diseases are largely subclinical, occur sequentially or concurrently, and are detected along with secondary diseases during diagnostic investigation. The vaccine repertoires for IBD and MD are greater than for CIA. The relative role of MD could increase in areas where MD vaccine and management are unable to control emerging virulent MDV strains with antigenic differences to existing vaccines.

Enteric viruses are increasingly recognized as ubiquitous in chicken and turkey production (191). Thus, ongoing challenge by one or more of the enteric viruses can be anticipated with horizontal and possible vertical transmission. The circumstances that determine clinical or subclinical expression are largely not defined, but the emerging evidence is that one or more of the enteric viruses are immunosuppressive. Characterizations of the enteric viruses, their pathogenesis singly and in combination, and methods for prevention and control merit further study.

The utilization of feed grains for ethanol production yields coproducts that will be used in feeds for livestock (272) and poultry. Distillers’ dried grains with solubles have reduced nutritional value and concentrated mycotoxins relative to the original grain. This emerging issue will impact poultry production, although to what degree is not known. Subclinical immunosuppression from nutritional and toxicologic causes is one possible effect.

\textbf{REFERENCES}

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