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CHICKEN INFECTIOUS ANAEMIA VIRUS: AN IMMUNOSUPPRESSIVE PATHOGEN OF POULTRY - A REVIEW

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ABSTRACT

Chicken infectious anaemia (blue wing disease) is an emerging highly contagious acute disease of poultry especially of young chicks, Characterized by anaemia ,atrophy of lymphoid organ and immunosuppression, Chicks 1-2 weeks old are more susceptible and more common in Broilers, It has a worldwide distribution and causes high

Introduction

Chicken infectious anaemia is also known as avian anaemia infection, blue wing disease, anaemia dermatitis syndrome and haemorrhagic aplastic anaemia syndrome. It is a highly contagious viral disease of chicken cause by Chicken Infectious Anaemia Virus (CIAV) which is characterized by anaemia, atrophy of lymphoid organs and immunosuppression. Immunosuppression induced by the virus increases the susceptibility of the infected chicks to secondary infections, and depresses their vaccine immunity and production performances in the field situations. Chicken is considered as the only natural and experimental host for Chicken Infectious Anaemia Virus (CIAV), even though antibodies have been detected from quails and the virus has been isolated from turkeys. Chicken infectious anaemia has been reported in Japan, Germany, United Kindom, United State of America, Australia, New Zealand and South African. Chicken infectious anaemia has been

economic losses due to poor growth, increased mortality, carcass condemnations and cost of antibiotics. Seroprevalence study has revealed 88.9% prevalence in Nigerian indigenous chickens and 99.3% in Nigerian commercial chicken. Chicken infectious anaemia is caused by an etiological agent known as the chicken infectious anaemia virus (CIAV), is the smallest known avian pathogen. CIAV is highly contagious, hardy virus that belongs to the Gyrovirus genus of the family Circoviridae and ubiquitous and can be vertically transmitted. Circular viral genome (2.3 kb) encodes three distinct viral proteins: VPl, VP2 and VP3. VPl is the major capsid protein and VP2 is a non-structural scaffold protein. VPl and VP2 are the protective proteins inducing neutralizing antibodies. VP3 is an apoptin, whose ability to induce tumour-specific apoptosis makes it a promising candidate for gene therapy of various tumours. The disease is characterized by generalized lymphoid atrophy particularly of the thymus, pale bone marrow and liver, anaemia, and severe immunosupression leading to secondary infections. Only a single viral serotype is believed to exist with high sequence identity among different isolates. Tentative diagnosis can usually be made based on flock history, clinical signs, and gross lesions in affected birds. Confirmatory diagnosis needs isolation and identification of the CIAV. Recent DNA detection techniques of PCR, alongwith RE analysis and sequencing have emerged as effective confirmatory tools for studying its molecular epizootiology. Boosting of parenteral immunity is top priority under control measures. Vaccination strategies inclusive of live-attenuated, inactivated and recombinant (r)-DNA vaccines are being explored. The disease has been reported in Nigeria, warranting the need for ascertaining epidemiological status of the disease in the entire country and devise effective control measures timely for this emerging disease.

Keywords: *Infectious. Anaemia Virus. Pathogen. Poultry. Review.*

reported in Nigeria. (Adair, 2000). Seroprevalence study has revealed 88.9% prevalence in Nigerian indigenous chickens (Emikpe *et al.*, 2005) and 99.3% in Nigerian commercial chicken (Oluwayelu, 2015). This

warrants the need for determining the epidemiological status of the disease in the country and emphasizing research on this pathogen. The aim of the present paper is to present an updated review on etiopathogenesis, epidemiology, immunosupression, diagnosis, treatment and control strategies for CIA.

HISTORY AND ECONOMIC IMPACT OF CHICKEN INFECTIOUS ANEMIA

Chicken infectious anemia was first recognized as a new disease in young chickens caused by a novel virus agent. The virus was isolated unexpectedly from commercial chickens during investigation of a Marek's disease vaccine accident caused by reticuloendotheliosis virus in Japan in 1974 (Yuasa *et al*., 1979). The newly described condition was associated with increased mortality in very young chickens that was characterized by severe anemia, lymphoid depletion, yellow to white bone marrow, atrophy of the thymus and bursa of Fabricius and hemorrhage (Yuasa *et al*., 1979). Infection with Chicken Infectious Anaemia Virus (CIAV) poses a serious economic threat especially to the broiler industry and the producers of specific-pathogen-free (SPF) eggs. Economic losses due to CIAV infections arise from poor growth, increased mortality and the cost of antibiotics used to control secondary bacterial infections (McNulty, 1991). It has been reported that net income per 1000 birds, feed conversion ratio and average weight per bird were lower in flocks with antibodies to CIAV compared to those without antibodies (McNulty *et al*., 1991). In addition, McIlroy *et al.* (1992) reported a loss of net income of about 18.5% due to decreased weight at processing and increased mortality in CIAV-infected birds.

ETIOLOGY

CIAVis an icosahedral naked virus with circular single stranded (ss)-DNA genome belonging to *Gyrovirus* genus of the family *Circoviridae.* It is the smallest avian pathogen (2.3 Kb genome; 23-25 nm diameter; 32 capsomers). The virus is very hardy and possesses remarkable thermostability (can withstand 80°C *115* min) and chemical stability (resist various physico-chemical agents): ether, chloroform, acetone and common disinfectants. PH 3.0 and lipid soluble. Inactivation of the virus requires heating at a temperature of 100°C for 15 min. There is only one

serotype existing worldwide and the apathogenic isolate does not exist. The virus shows high nucleotide sequence identity (limited genetic variability) among different isolates. The major economic loss caused by this virus is due to disease outbreaks associated with secondary bacterial/viral infections because of its immunodepressive nature. The virus replicates in the nucleus of haematopoietic and thymic precursors and multiplies via *"Rolling circle model".* Viral genome consists of three overlapping major open reading frames (ORFs) -ORFl/ C1, *ORF-2/C2* and *ORF-3/C3* encoding three putative viral proteins VP1, VP2 and VP3, respectively. VP1 and VP2, both are necessary for the formation of neutralizing and protective antibodies.
(Bhatt *et al.,* 2011).

EPIDEMIOLOGY

CIA is having worldwide distribution and has attained the status of an emerging and immunosuppressive disease affecting chickens. The disease has been reported from many countries viz. Japan, Germany, Sweden, UK, Thailand, Canada, USA, Australia, France, Brazil, South Africa, Argentina; New Zealand, Chile, Hungary, China, Mexico, Slovenia, Nigeria, Israel, Greece, India. The epidemiology of CIAV is complex as the development of clinical disease following infection depends on a number of factors including age of bird, challenge dose of virus, route of infection, secondary invaders and presence of maternal antibodies (Oluwayelu, 2008). Another key factor is co-infection with other immunosuppressive viruses such as Marek's disease virus (MDV), infectious bursal disease virus (IBDV), reticuloendothelial virus (REV), adenovirus and reoviruses (Yuasa *et al*., 1979; Bhatt *et al.,* 2011).

PATHOLOGY

Chicken is the only natural host of the virus with all ages susceptible to CIAV infection, most susceptible age being chicks 1-2 wks. Age associated resistance develops for the clinical disease in chicks after 2-3 weeks of age due to imunocompetence. Vertical transmission occurs when breeders with no antibody to CIAV or with no previous exposure to the virus become infected as they come into lay. In breeders, clinical manifestations are not evident, but the virus is vertically transmitted to

the offsprings. The infection acquired last for a short period and elimination of CIAV occurs within 4-6 weeks with no evidence of latency. However, wide distribution and long persistence of CIAV in the reproductive tissues of infected chickens has been reported, indicating CIAV can be vertically transmitted from persistently infected hens. Horizontal infections do occur by direct or indirect contact with the virus surviving in poultry houses. Experimentally, CIAV can be transmitted by inoculation of the virus in susceptible day-old chicks by intramuscular or intraperitoneal routes (Renshaw *et al.,* 1996).

PATHOGENESIS

By adsorption and penetration, CIAV enters the target cell and multiplies in the nucleus by a rolling circle model. The virus causes aplastic anaemia in young chickens as a result of destruction of erythroblastoid cells, thymus atrophy and immunodeficiency owing to severe depletion of thymocytes, and hemorrhages in the muscle and subcutaneous tissues. CIAV has specific tropism for lymphocytes which is responsible for lymphocyte depletion. Virus mainly attacks thymic lymphoblasts and haemocytoblast. The virus replicates primarily in hematopoietic precursor cells in the bone marrow and thymic precursor cells in the cortex region of thymus, where it leads to cytolytic infection and cell death by apoptosis. Erythropoiesis, myelopoiesis and lymphopoiesis are adversely affected leading to clinical pictures of anaemia, thrombocytopaenia and leucopenia. The thymocyte infection causes chromatin aggregation, fragmentation of cellular DNA into oligonucleosomes, karyorrhexis and cell death via apoptosis, with the presence of VP3-induced apoptotic bodies. Isolates of CIAV identified so far do not differ significantly in pathogenicity and the ability of the virus to produce anemia is directly related to its dose, age of the bird and presence of secondary invaders. Convalescent stage coincides with antibody development and birds recover from depression / anaemia by 4-5 weeks. Body weight gradually returns near to normal by 5-6 wk but chicks remains stunted. Affected birds, if coinfected with other viruses such as MDV, IBDV, reovirus, REV and NDV develop marked immunosuppression leading to synergistic effects of both the agents. (Dhama *et al.,* 2008).

IMMUNOSUPPRESSION

CIAV is a potent immunosuppressive agent and produces generalized lymphoid atrophy in young chicks and especially suppresses the population of T lymphocytes in the thymus. In newly hatched chickens, CIAV transiently causes severe anaemia due to destruction of erythroblastoid cells and immunodeficiency due to depletion of cortical thymocytes. The immunodepression dramatically leads to susceptibility of birds to secondary infections of viral, bacterial or fungal origin; depressed vaccinal immunity against poultry pathogen like Marek's Disease (MD), Newcastle Disease (NCD), Fowl Pox (FP), Infectious Laryngotracheitis (ILT), etc.; enhanced vaccination reactions. If secondary complications with other poultry pathogens occur, then there is profound immunosuppression, which can even overcome age and maternal antibody resistance, increase in the susceptibility and persistency period in immunocompromised chicks, disease potentiation exacerbated signs and lesions, increased mortality and retarded recovery. In experimentally infected 1-day-old chicks, the depletion of their thymus is at its maximum 2 weeks after infection (Velmurugan, 2006). When the thymus sections of these chicks are stained with a monoclonal antibody (Mab) specific for CIAV, positive cells are detected only in the cortex. The number of infected cells is at its maximum at 6 to 7 days after infection; it takes several days before infected cells appear and, again, several days before the entire cortex is depleted. Chickens older than 3 weeks of age are still susceptible to infection but do not develop disease, infected cell or thymus depletion at this age could not be detect , which may have been caused by the fact that only a few thymus lobules are affected and not the cortex of all thymus lobules. In chickens infected at 6 weeks of age, infected cells were detected in the cortex of one thymus lobule in two out of 10 infected animals. The differences in susceptibility for the disease of very young and chickens older than 3 weeks is an intriguing one, suggested that it may be caused by lack of susceptibility of thymic precursor cells after hatching.(M. Noteborn and Koch 1995; Velmurugan B 2006).

TRANSMISSIONS

Both vertical and horizontal transmission occurs and the most important one is vertical transmission which occurs from parents to the offspring through the hatching eggs while horizontal from bird to bird(direct contact) and environment to birds through contaminated faeces(indirect contact). (Dhama *et al.,* 2002)

CLINICAL SIGNS

Clinical picture of disease is characterized by aplastic anaemia, generalized lymphoid atrophy, haemorrhages, increased mortality, immunosuppression and secondary complications. CIAV infected chicks show general signs of weakness, anorexia, ruffled feathers, anaemia (pallor) and stunting. There is drop in haematocrit values (PCV < 25%) and blood becomes paler and watery. Mortality is generally 5 - 10% (within 2-4 weeks), which can go even up to 60% in secondary complications. If the affected bird survives, they completely recover from anemia by 4-5 weeks after infection. Secondary infections causing more severe clinical signs are frequently observed in field conditions (Velmurugan, 2006).

ECONOMIC CONSEQUENCES OF CIAV INFECTIONS

The immunosuppressive effects of CIAV on broilers are economically significant. CIAV is immunosuppressive, affected flocks suffer from an increase of opportunistic and/or secondary infections. Broilers may perform badly due to poor feed conversion and reduced weight gain. It has been proven that even flocks that may appear normal but suffered from a subclinical CIAV infection performed less well when compared to flocks that remained negative throughout the growing period. Also infections may result in increased condemnation rates at slaughter (Mc Nulty *et al*., 1991).

The effect of a subclinical CIAV infection on the performance parameters of broilers was well documented by Mc Nulty *et al*., (1991).

Effect of CIAV infection on Performance - % of deviation from the commercial average

Flock CIAV status	% net income	Bonus %	Feed conversion	Weight %	Mortality %
-	+2.4	+2.7	-0.4	+0.8	-0.16
+	-10.6	-8.8	+1.6	-1.7	+0.24

GROSS LESIONS (POSTMORTEM LESIONS)

Gross lesions include generalized lymphoid atrophy particularly of thymus, which is the most consistent lesion, pale and fatty bone marrow, which is the most characteristic lesion. The femur bone is most commonly evaluated for this pathognomonic finding. Liver becomes swollen and mottled with pale/yellowish discoloration. Visceral organs also show areas of congestion and hemorrhages during infection. (M. Noteborn and Koch 1995; Oluwayelu *et al.,* 2005). Focal lesions (mostly in the wings) appear as ecchymotic skin haemorrhages. The lesions turn blue and may break, releasing serosanguineous exudate which is prone to secondary bacterial infections, leading to gangrenous dermatitis. This can be especially notorious at the end of the wings, hence the name "Blue Wing Disease" used to describe this condition. The tips of the wings may appear haemorrhagic and necrotic. The mortality peaks 5 -6 days after the appearance of the clinical signs, declining to normal 5 – 6 days later. Thymus atrophy with lobes appearing small and greyish. When observed closely, the medullar part of the lobes predominate over the cortical part. Bone marrow atrophy. When observed closely it appears pale (Oluwayelu *et al.,* 2005).

HISTOLOGY

Bone marrow

In the bone marrow a decrease in the number haematopoietic cells is observed 4 – 6 days post infection. This is followed by the appearance of large blastic cells. The haematopoietic tissue is replaced by adipose tissue; this gives the bone marrow a pale appearance (M. Noteborn and Koch 1995; Oluwayelu *et al.,* 2005).

Other organs

Depletion of lymphocytes from the thymus, spleen, Bursa Fabricius and caecal tonsils is observed, followed by hyperplasia of reticular cells. Changes in the thymus appear at 4 days post infection, with cortical lymphocytes disappearing and being replaced by reticular cells. Medullar lymphocytes are also reduced. Recovery starts 20 days post infection in convalescent birds.

The changes found in the different organs suggest that CIAV multiplies in the lymphocytes (Oluwayelu *et al.*, 2005).

Fig. 1.CIAV Gross/Postmortem Lesion: Hemorrhagic lesion on the wing of a chicken with CIA (http://www.chicken-anemia.com/disease/haemorrhage-wing.asp)

Fig. 2.CIAV Gross/Postmortem Lesion: echymotic hemorrhages on the inner wings surface of an infected chicken. (http://www.chicken-anemia.com/disease/blue-hock.asp)

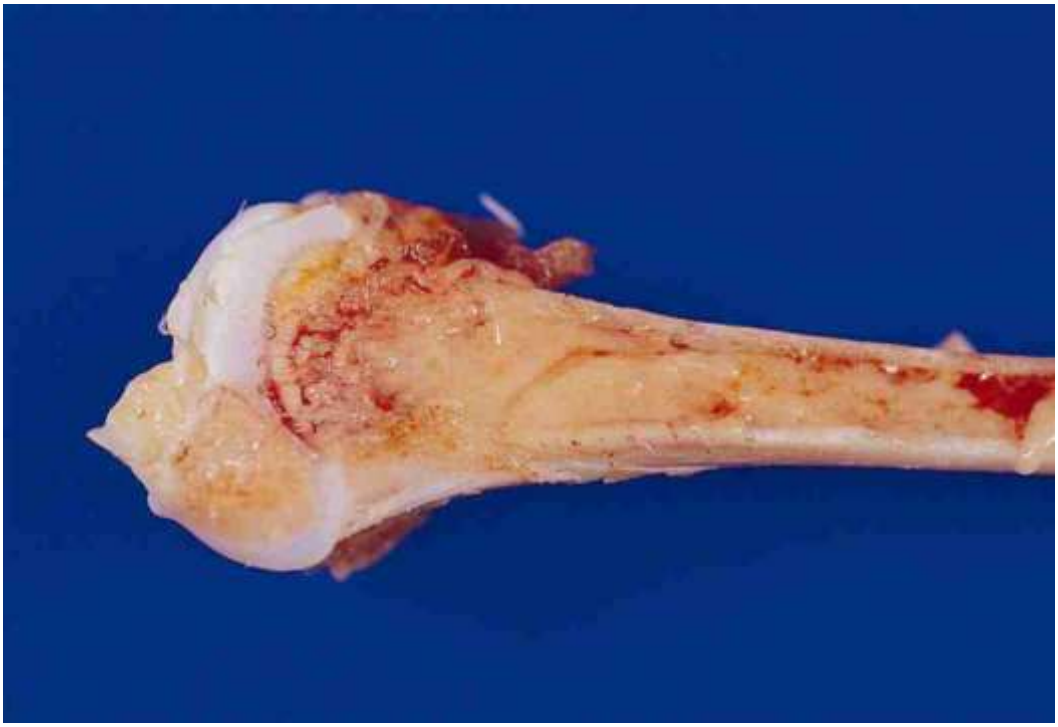

Fig. 3.CIAV Gross/Postmortem Lesion: anaemia resulting from infection of haemocytoblasts in the bone marrow (www.PoultryMed.com)

Fig. 4.CIAV Gross/Postmortem Lesion: Pale comb in 6 weeks pullet due to severe anaemia
www.PoultryMed.com

Fig. 5.CIAV Gross/Postmortem Lesion: Subcutaneous haemorrhage in a young chicken with Chicken Infectious Anemia, resulting in blue discoloration of the hock joint.
(http://www.chicken-anemia.com/disease/blue-hock.asp)

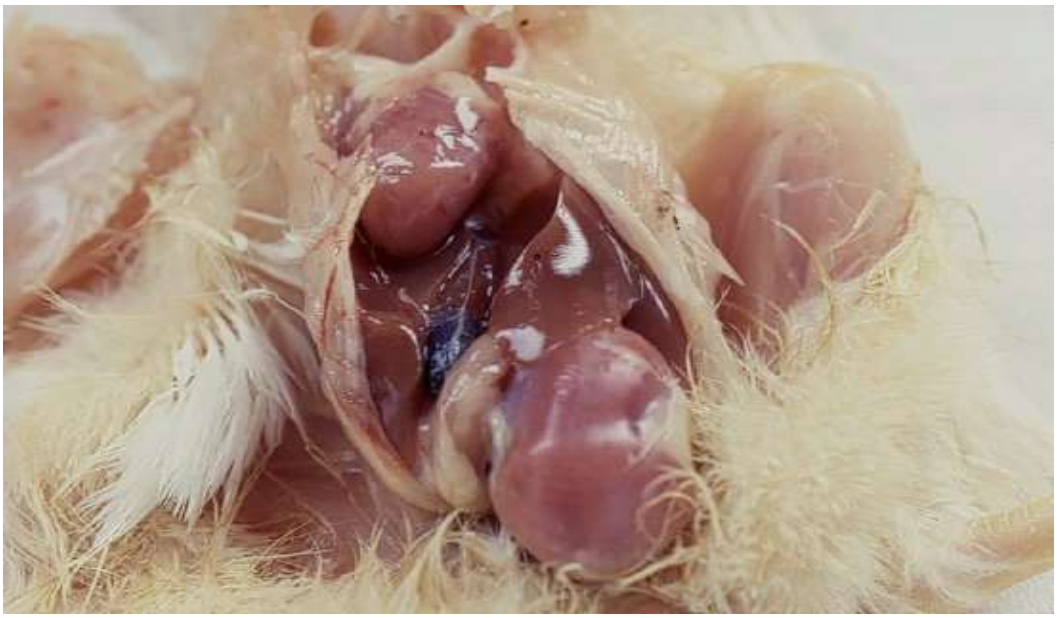

Fig. 6.CIAV Gross/Postmortem Lesion: Pale anemic carcass of a young chicken with Chicken Infectious Anemia
http://www.chicken-anemia.com/disease/pale-carcass.asp

Fig. 7.CIAV Gross/Postmortem Lesion: Subcutaneous haemorrhages and petechiae in the breast muscle of a young chicken with Chicken Infectious Anemia.
http://www.chicken-anemia.com/disease/sc-haemorrhages.asp

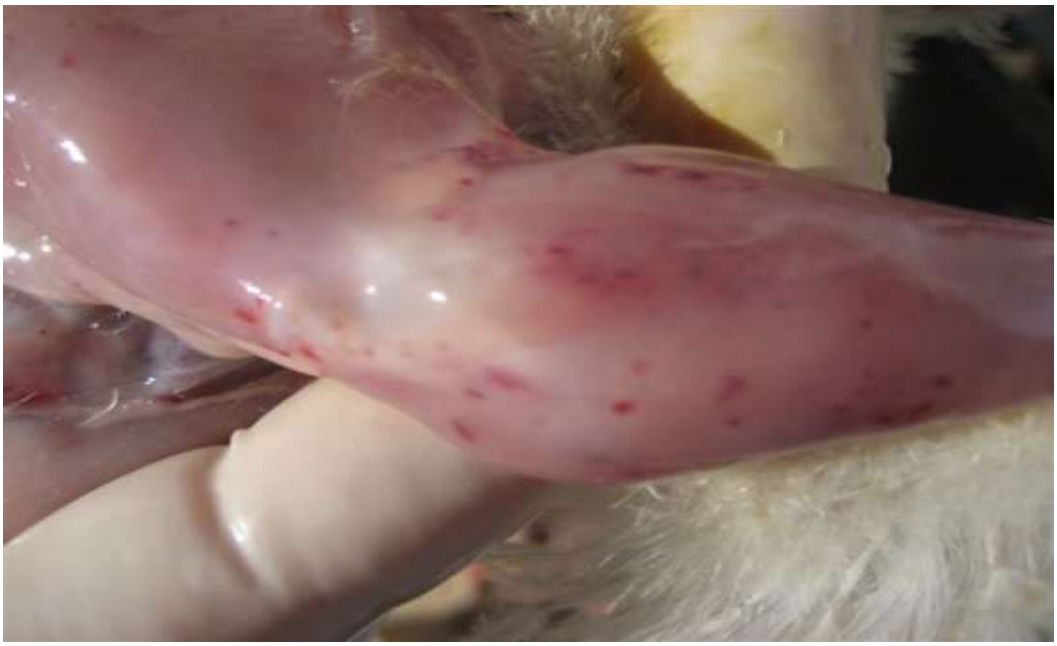

Fig. 8.CIAV Gross/Postmortem Lesion: Subcutaneous petechiae haemorrhages on the hock of a young chicken with Chicken Infectious Anemia.
http://www.chicken-anemia.com/disease/sc-haemorrhages.asp

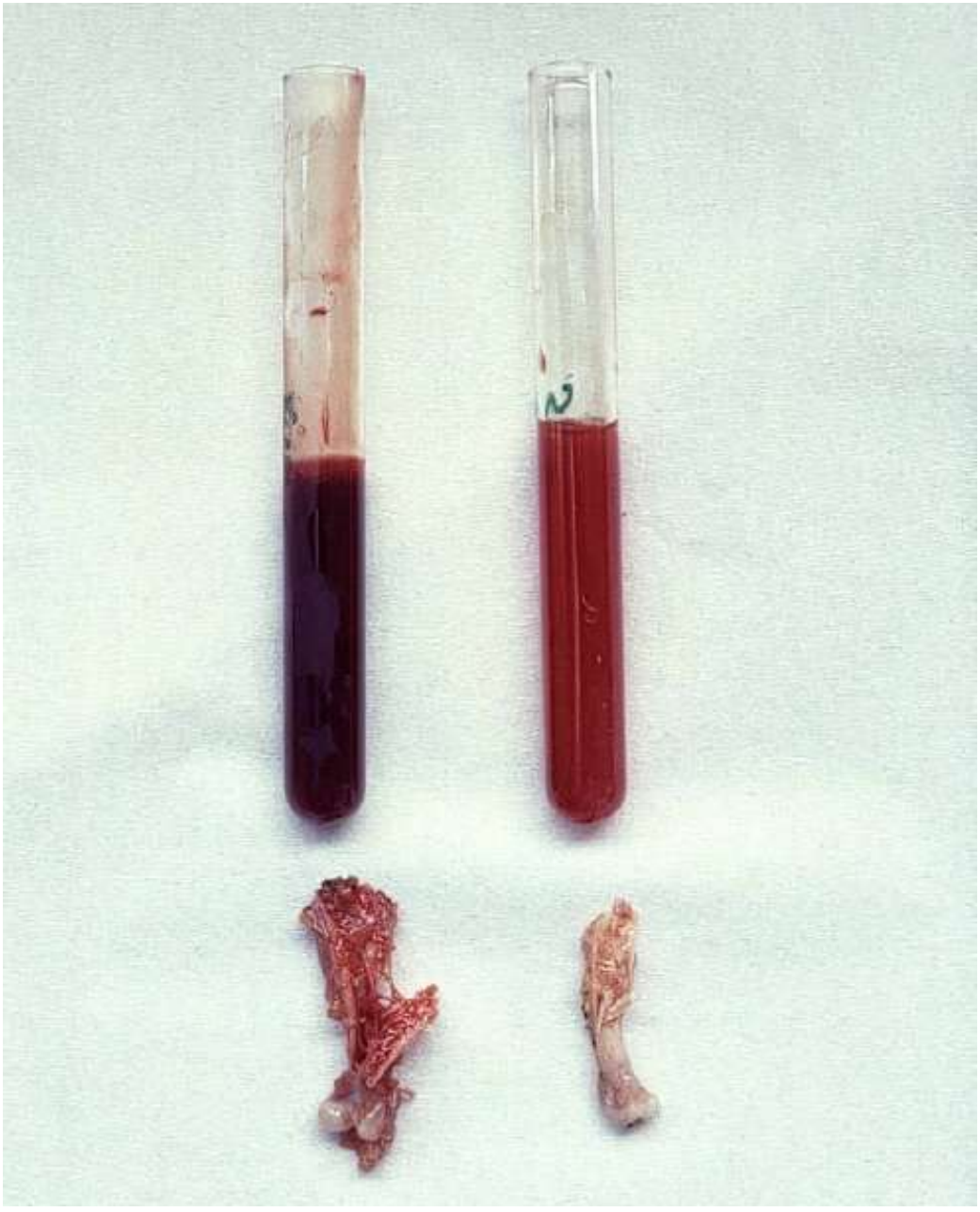

Fig. 9.CIAV Gross/Postmortem Lesion: Pale bone marrow and watery blood in a chicken with Chicken Infectious Anemia (right) compared to that of a normal chicken (left).
http://www.chicken-anemia.com/disease/bone-marrow-atrophy.asp

DIAGNOSIS

A preliminary or tentative diagnosis of the infection is based on the typical clinical signs and post-mortem lesions. Paleness and anemic appearance with depression as clinical signs and enlargement of liver,

paleness of kidney, atrophy of thymus and paleness of medulla of long bones as lesions, are quite suggestive of CIA. The typical CIA pathology and knowledge of the parent flock serology can help in the diagnosis. For serological detection, ELISA, VNT and FAT are the most commonly employed techniques. Commercial ELISA kits detecting antibodies are available for flock screening (Dhama *et al*. 2008; Oluwayelu, 2009). PCR endowed with sensitivity and specificity has been proven to be very useful for CIAV-DNA detection in a variety of clinical or field samples (Oluwayelu *et al*., 2007). High and specificity PCR is also very effective for the early detection of CIAV in cell lines or infected tissues of the affected birds (Oluwayelu *et al.,* 2008). Clinical specimens aseptically collected to detect the infection are liver, spleen, thymus, femur bone, bursa in 10% formal saline for histopathological examination, and in 50% buffered glycerol for virus isolation. Materials need to be sent under frozen condition or on ice immediately for virus detection/isolation. Sera samples should be collected for ascertaining the CIAV antibodies in the respective samples (Bhatt *et al*., 2011; Dhama *et al*. 2008; Oluwayelu, 2015).

DIFFERENTIAL DIAGNOSIS

Runting and Stunting Syndrome, field rickets and Salmonella enteritidis septicaemia were the conditions most likely to produce low weights and mortality in this age group. All of these were excluded on the absence of typical pathology. Also infectious laryngotracheitic (Schat *et al*., 2003; Oluwayelu 2009).

TREATMENT

There is no specific treatment. Secondary bacterial infections may be treated with antibiotics and minimized through good hygiene and management.
(Dhama *et al.* 2006; Ducatez *et al.,* 2008).

PREVENTION

Prevention strategies include vaccination, general hygiene and Regular seromonitoring is important for screening breeder flocks so as to prevent clinical outbreaks and vertical transmission. Live attenuated

vaccines are used for either injection or drinking water administration for breeder flocks prior to the start of laying (Renshaw *et al.*,1996). This is usually done between 12 and 15 weeks of age to allow time for seroconversion. Direct use of infected material (litter or tissue homogenates from infected birds) to infect flocks prior to breeding, again allowing time for seroconversion, has also been used. Serological testing may be used to ascertain seroconversion.(Schat and Van Santen 2003; Ducatez, *et al.* 2006).

CONTROL

Boosting of parenteral immunity is the top priority under control measures. The control of other diseases e.g. Marek's Disease (MD), Newcastle Disease (NCD), Fowl Pox (FP), Infectious Laryngotracheitis (ILT) and Infectious Bursa Disease (IBD), etc. that suppress the immune system is also important because of their synergism with CIAV. (Soine *et al.* 1994).

CONCLUSION

In conclusion, based on the seroprevalence and prevalence studied conducted on commercials and Nigeria indigenous rural poultry respectively and others similar studies on CIA in the country, the presences of CIA have been established and confirmed in the country.

RECOMMENDATIONS

Being potentially immunosuppressive pathogen, causing considerable health problems and economic losses in the poultry industry, CIAV should be taken into consideration while making diagnosis of diseases in the clinics and the fields. Proper attention should also be paid towards early diagnosis, regular serominotoring as well as formulating suitable control strategies including stringent biosecurity measures. Proper epidemiological survey need to be followed to know the real magnitude of the infection in the country. Focused approach on CIAV research and diagnosis will help devising effective and timely control strategies.

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(http://www.chicken-anemia.com/disease/blue-hock.asp): CIAV signs: echymotic hemorrhages on the inner wings surface of an infected chicken.

(http://www.chicken-anemia.com/disease/blue-hock.asp): CIAV signs: Subcutaneous haemorrhage in a young chicken with Chicken Infectious Anemia, resulting in blue discoloration of the hock joint.

(http://www.chicken-anemia.com/disease/bone-marrow-atrophy.asp): Pale bone marrow and watery blood in a chicken with Chicken Infectious Anemia (right) compared to that of a normal chicken (left).

(http://www.chicken-anemia.com/disease/haemorrhage-wing.asp): CIAV signs: Hemorrhagic lesion on the wing of a chicken with CIA

(http://www.chicken-anemia.com/disease/pale-carcass.asp): Pale anemic carcass of a young chicken with Chicken Infectious Anemia

(http://www.chicken-anemia.com/disease/sc-haemorrhages.asp): Subcutaneous petechiae on the hock of a young chicken with Chicken Infectious Anemia.

(http://www.chicken-anemia.com/disease/sc-haemorrhages.asp): Subcutaneous haemorrhages and petechiae in the breast muscle of a young chicken with Chicken Infectious Anemia.

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