PATHOLOGY OF THE RABBIT

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General Information
- Classified in the Order Lagomorpha
- Over 100 different breeds
- Descendants of the European wild rabbit
- Differ from rodents because of additional pair of incisor teeth directly behind the upper incisors
Cardiovascular System
- Chambers on right side are thin
- Clotted blood common in the right ventricle without any evidence of contraction
- The right atrioventricular valve is bicuspid

Gastrointestinal System
- Hindgut fermenters
- Cecotrophy
- Teeth grow continuously
- GI tract long, contents are 10-20% of body weight
- Abundant gut-associated lymphoid tissue, makes up 50% of the lymphoid mass (Sacculus rotundus)

Gastrointestinal System
- Rapid gut transit time
- Feed early morning and evening and at night
- Do not vomit
Urinary Tract

- Kidneys are unipapillate
- Urine is the major route of calcium and magnesium excretion
- Urine contains many crystals which forms a thick sediment
- Normal urine color can vary from yellow to red

Reproductive Tract

- Females are does; males are bucks
- Breeding lifespan is 3-4 years
- Uterus lacks a body, has two separate uterine horns with two cervices
- Induced ovulators
- Hemochorial placentation
- Gestation 25-29 days, 4-10 kits

Hematolymphatic System

- Prominent marginal ear veins
- Polychromasia normal
- Heterophils are the neutrophil counterpart
- Lymphocytes are predominant circulating leukocyte
- May have large numbers of circulating basophils
VIRAL DISEASES

Myxomatosis

- Leporipoxvirus
- Two subtypes
- Direct or indirect contact
- Fleas and ticks

Image courtesy of Dr. King/Cornell University
Stellate cells with intracytoplasmic inclusion bodies in a loose collagenous matrix with inflammatory cells.

Shope Fibroma
- Causative agent also a leporipoxvirus
- Virus transmitted by fleas and ticks
- Cottontail is the natural host
- Lesions primarily on legs and feet
- Immunocompromised have systemic disease
Cutaneous Papillomatosis

- Etiologic agent is a papilloma virus
- Benign disease of cottontail rabbits
- Typical viral squamous papilloma
- Most spontaneously regress
- Some may progress to squamous cell carcinoma

Cutaneous Papilloma

Cutaneous Papilloma
Oral Papillomatosis

- Also caused by a papilloma virus
- White, fleshy, exophytic masses along the ventral margin of the tongue
- Spread by direct contact in areas with mucosal damage
- Typical virus papilloma

Rabbit Pox Virus

- Orthopoxvirus
- Aerosol transmission
- Potential animal model for smallpox
- Viral replication in lymphoid tissue
- Papular lesions in skin and mucocutaneous sites with systemic disease

Ulcerative glossitis
Leporid Herpesvirus 4

- Veterinary Pathology, May 2008
- Alaska
- Clinically resembled myxomatosis
- Ocular and anogenital skin necrosis with lymphoid necrosis
- Viral intranuclear inclusion bodies + syncytial cells

Leporid Herpesvirus 4

- Single case in Canada, 2010
- Pet NZW rabbit housed outdoors
- Necrosis, vasculitis, and intranuclear viral inclusions in spleen, lungs, skin and ileum
- Canadian Veterinary Journal 2010; 51:1383-1386

Human Herpesvirus 1

- Zoonotic disease
- Herpes simplex virus
- Rabbits extremely sensitive to infection
- Meningoencephalitis
- Inclusions in neurons and astroglial cells

Leporid herpesvirus 3

- Gamma herpesvirus
- Cottontail rabbits
- Juveniles
- Lymphoproliferative disease

Rabbit Coronavirus

- Related to human coronavirus strain 229E
- Pleural effusion
- Cardiomyopathy
- Enteritis
Rabbit Rotavirus
- Mild to severe diarrhea
- Direct contact
- Clinically normal rabbits often have titers
- Villar atrophy, blunting and fusion
- Clinical signs worse with secondary infections

Rabbit Viral Hemorrhagic Disease
- Lagovirus, family Caliciviridae
- Reportable disease in the U.S.
- 4 recent outbreaks
- Transmitted by direct contact, carriers possible
- Predilection for hepatocytes and monocytes
- Disease course usually peracute to acute, but some subacute cases

Found dead with epistaxis

Pulmonary Hemorrhage
Splenomegaly
Periportal hemorrhage and necrosis
Necrohemorrhagic enteritis

Novel Rabbit Calicivirus (Michigan)
- 79% similarity with RVHD virus
- Could not induce experimental disease

From: Emerg Inf Dis, Vol.15, No.12
### Rabies Virus
- Enzootic raccoon-variant
- Outdoor housed
- Paralytic form
- No gross lesions
- Histology: nonsuppurative meningoencephalitis with Negri bodies

### BACTERIAL DISEASES

#### Pasteurellosis
- Most significant disease of rabbits
- *Pasteurella multocida*
- Direct contact
- Aerosols probably not important form of transmission
- Seasonal incidence
- Predisposing factors

#### Pasteurellosis
- Bacteria is present in the upper respiratory tract
- Spread to lungs by aerosol droplets
- Goes to middle ear via eustachian tube
- Can spread hematogenously to many locations in the body
Clinical Disease due to *P. multocida*

- Rhinitis
- Atrophic rhinitis
- Pneumonia
- Otitis media/interna
- Encephalitis
- Abscesses
- Mastitis
- Dermatitis
- Metritis
- Septicemia

Fibrinous Tracheitis
Atrophic Rhinitis

Fibrinous Tracheitis
Fibrinous Tracheitis

- Multiple pulmonary abscesses
- Abscess in the abdominal cavity

Pasteurellosis Histopathology

- The hallmark is heterophilic inflammation
- With chronic cases, more lymphocytes and plasma cells, multinucleate giant cell macrophages, fibrosis
- Chronic pneumonia: type II pneumocyte hyperplasia
Bordatelllosis

- *Bordatella bronchiseptica*
- Often present with *P. multocida*
- Does it cause primary pneumonia?
- Chronic pneumonia with bronchiolitis and perivascular lymphocytes, plasma cells and macrophages

Staphylococcosis

- *Staphylococcus aureus*
- Individual infections or colony problem
- Wide range of clinical disease
- Transmitted by direct contact
- Carriers

Ulcerative Pododermatitis

- “Sorehock”
- Overweight males, wire-floor cages
- Plantar surface of metatarsal and/or metacarpal regions
- Gross: Ulcerative, focal, cutaneous lesion

Photo courtesy: Dr. Scot Estep
Mastitis

- "Blue Breast"
- More common in recently kindled and heavily lactating
- Orphan young can spread infection
- May lead to fatal septicemia
- Other causes: *P. multocida, Streptococcus*
Septicemia

- Usually in the very young
- Suppurative lesions
- Lung, kidney, spleen, heart

Suppurative, vegetative valvular endocarditis

Suppurative nephritis with infarcts

WSC 2012-2013, Conference 7, Case 1
Treponematosis

- *Treponema paralucuniculi*
- Rabbit syphilis or vent disease
- Generally self-limiting
- Erythema and edema at mucocutaneous junctions
Warthin-Starry: helical bacilli

Clostridiosis

- *C. perfringens*, *C. difficile* and *C. spiroforme*
- Concurrent infections with other bacteria and protozoa cause proliferation
- Peracute to chronic clinical presentations

Clostridium spiroforme

- Most common of the clostridial infections in rabbits
- Type E iota toxin
- Infections are common
- Peracute: death, no prior illness
- Chronic: anorexia, wasting, diarrhea

Perineal soiling with bloody diarrhea

Necrotizing enteritis
Dilated cecum with liquid green-brown fecal material

Courtesy: Dr. King, Cornell University
**C. difficile**
- After antibiotic administration or dietary change
- Lesions mostly involve the ileum

**Tyzzer’s Disease**
- *Clostridium piliforme*
- Predisposing factors
- Interspecies transmission
- Acute disease
- Classic triad of gross lesions
Silver stain: filamentous intracytoplasmic bacilli

Colibacillosis

- Enteropathogenic strains
- Attaching and effacing
- Rapid proliferation with change in intestinal pH
- Most severe in weanling rabbits
- Intestinal atrophy, blunting and fusion

Scanning Electron micrograph

Bacilli are adhered to intestinal villi

8/5/2013
**Proliferative enteropathy**

- *Lawsonia intracellularis*
- Suckling, weanling and adults
- Mostly acute
- Terminal small intestine, cecum, colon
- Three forms:
  - Erosive
  - Suppurative
  - Proliferative

Transmission Electron micrograph

Thickened colonic mucosa

Warthin-Starry
Yersiniosis

- *Yersinia pseudotuberculosis, enterocolitica*
- Contaminated food and water
- Wild birds and rodents
- Clinical signs nonspecific

Tularemia

- *Francisella tularensis*
- “Rabbit Fever”
- Direct contact and insect vectors
- Found dead

Necrosis liver, spleen, cecum, lymph nodes
Listeriosis

- *Listeria monocytogenes*
- Contaminated feed and/or water
- Hepatic necrosis
- Meningoencephalitis
- Reproductive problems

Cilia-Associated Respiratory Bacillus (CAR) Bacillus

- Subclinical infections
- Mouse and rat isolates do not infect rabbits
- Colonizes ciliated epithelial cells

Mycobacteriosis

- Natural infections rare
- *Mycobacterium bovis, M. avium* and *M. tuberculosis* reported
- Animal model of human disease
**Mycobacteriosis**

- *Veterinary Pathology* 46:1000-1002
- Single case report of granulomatous pneumonia in a dwarf rabbit
- Intra-alveolar foamy macrophages and giant cells with expansion of the interstitium by lymphocytes/plasma cells
- Identified *Mycobacterium genavense* on PCR

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**Rabbit Model of Pulmonary TB**

- Latent tuberculosis infection
- Aerosol infection with *M. tuberculosis* strain CDC1551
- Spontaneously cleared infection by 20 weeks
- Infection could be reactivated with corticosteroid administration

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**Ringworm**

- *Trichophyton mentagrophytes*, *Microsporum canis* and *M. gypseum*
- Carriers
- Head, ears and feet
- Young and immunocompromised

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**MYCOTIC INFECTIONS**
PROTOZOAL/MICROSPORIDIAL DISEASES

Encephalitozoonosis

- *Encephalitozoon cuniculi*
- Widespread infection in rabbits
- Dwarf rabbits
- Three major forms:
  - Neurological
  - Ocular
  - Renal

Transmission is mostly through ingestion of urine contaminated with infective spores
- Transplacental transmission is possible
- No gross lesions in the CNS; distinctive gross lesions in the kidney
Gram Stain
**Toxoplasmosis**
- Differential for Encephalitozoon
- Disease in lab rabbits rare
- Enteritis, lymphadenitis, splenomegaly and necrotizing hepatitis
- Necrosis with tachyzoites and/or cysts

**Intestinal Coccidiosis**
- Many species within Eimeria
- Most pathogenic: E. intestinalis and E. flavescens
- Common and widespread
- Co-pathogen
- Fecal-oral transmission
- Weanlings

Multifocal necrotizing splenitis
Hepatic Coccidiosis

- *Eimeria stiedae*
- Weanlings
- Most infections are inapparent
- Clinically: anorexia, weight loss, constipation or diarrhea
- GROSS LESIONS ARE CLASSIC !!!!!!!!
Ear Mites

- *Psoroptes cuniculi*
- Common
- Spend entire life on host
- Nonburrowing
- Distinctive clinical presentation
Fur Mites

- *Cheyletiella parasitovorax*
- Mild alopecia
- NOT pruritic
- Skin scrapings
Scabies

- *Sarcoptes scabei var cuniculi*
- Alopecia and dermatitis
- PRURITIC
- Face, nose, lips, external genitalia

Pinworms

- *Passalurus ambiguus*
- Fairly common
- Adults in cecum and colon
- Most are asymptomatic
Cestodes

- Rabbits are intermediate hosts
- *Taenia serialis* and *T. pisiformis*
- Subcutaneous tissues, mesentery, liver
Visceral Larval Migrans

- *Baylisascaris procyonis*
- Larval stages of the raccoon roundworm
- Progressive neurologic signs
- Also lesions in heart, liver and kidney

Vitamin E Deficiency

- Muscular soreness and stiffness
- Neonatal mortality and infertility
- Gross: pale streaks in skeletal and cardiac muscle
- Histo: myofiber degeneration and necrosis with mineralization
Vitamin D Toxicosis

- Rabbits are very sensitive to Vit. D
- Adults are more sensitive
- Nonspecific clinical signs
- Hypercalcemia
- Mineralization at multiple sites
- Osteodystrophy
Hypo and hypervitaminosis A

- Poor conception rates
- Congenital anomalies
- Fetal resorption
- Abortion
- Birth of thin, weak kits

Watanabe Rabbit

- Animal model of atherosclerosis
- Gene defect in LDL receptor
- Develop fulminant hypercholesterolemia
Carbohydrate Overload

- High starch, low fiber diets
- Bacterial proliferation
- Toxin production
- Diarrhea with loss of fluid into lumen
Mucoid Enteropathy

- Etiology: Multifactorial and incompletely understood
- Related to disruption of normal cecal environment
- Important cause of morbidity and mortality
- Gross and histologic lesions are characteristic

Mucoid Enteropathy - Pathogenesis

Dietary change
Stress
Cecal/Colonic Impaction
"cecal factor"
Systemic goblet cell hyperplasia

Mucoid Diarrhea
Pregnancy Toxemia

- Primiparous
- Obese
- Late in gestation
- Fatty infiltration of multiple organs
- Clinical pathology abnormalities

Chronic Fluorosis

- Veterinary Pathology, Sep 07, pp.703-706
- Osseous proliferations of extremities and mandible
- Proliferative gastroduodenopathy
- Bone fluoride levels of 12,700 and 15,000 µg/gm bone ash vs. 550 µg in controls

CONGENITAL CONDITIONS
Mandibular Prognathism
- Malocclusion
- Autosomal recessive
- 8-10 weeks
- Can also be an acquired condition

Congenital Glaucoma
- Buphthalmia
- Autosomal recessive
- Increased intraocular pressure

Splayleg
- Descriptive term
- Many causes
- Inability to adduct one or more legs
Endometrial Venous Aneurysm

- Blood-filled varices
- Rupture and bleed into the uterine lumen

Courtesy of: Dr. Asfaw, Duke University

Miscellaneous Conditions
Vertebral Fracture
- Skeleton extremely fragile
- Improper handling
- Lumbosacral region
- Spinal cord damage, paralysis

Trichobezzar
- “Wool Block”
- Common
- Usually incidental finding
- May cause partial or complete obstruction
Barbering

- Most common in young and group housed rabbits
- Boredom
- Low roughage diets

Urinary Tract

- Thick, dark yellow urine
- Calcium carbonate and triple phosphate crystals
- Susceptible to urinary calculi
Uterine Adenocarcinoma

- Most common spontaneous neoplasm of the rabbit
- Thickenings of the uterus
- Metastasis
- Serosal implantation
Endometrial Hyperplasia
- Common
- Usually in rabbits older than 3 years, but sometimes seen in younger
- Clinical signs: serosanguinous vaginal discharge and/or hematuria
- May have concurrent mammary lesions

Mammary Gland
- Mammary gland hyperplasia
- Dysplasia
- Carcinoma
Male Reproductive

- Testicular interstitial cell tumors most common
- Seminomas and Sertoli cell tumors have been reported

Nervous System

- Pituitary adenomas
  - Prolactin-secreting
  - Mammary gland changes
Musculoskeletal System
- Osteosarcomas
- Ossifying fibroma
- Rhabdomyosarcoma
- Leiomyosarcoma

Urinary System
- Nephroblastoma
- Renal cell carcinoma

Photo courtesy of Dr. Kim Whitten
Lymphoma
- Juvenile and young
- Visceral
- May be leukemic
- Both B and T cell types

Trichoblastoma
- Benign neoplasm of hair follicle origin
- Common
Interscapular Fibrosarcoma

- Fibrosarcoma at previous vaccination site
- Neoplasm recurred and rabbit euthanized
- Similar to vaccine-associated sarcomas in cats

Intraocular Sarcomas

- JVDI 21:547-551 (2009)
- Two cases, adult domestic rabbits
- Pleomorphic, intraocular spindle cell neoplasm expanding the globe
- Vimentin +, neg. for keratin, S100, desmin, sma
- Lens material within neoplasm
- No history of trauma to the affected eye in either case
GENERAL INFORMATION

Rabbits are classified in the Order Lagomorpha. They differ from rodents because they possess an additional pair of incisor teeth directly behind the large incisors of the upper jaw. There are over 100 different breeds of rabbits that are descendants of the European wild rabbit, *Oryctolagus cuniculus*. The majority of rabbits used in biomedical research are New Zealand white rabbits.

The chambers of the right side of the heart are relatively thin and frequently a quantity of clotted blood will be found in the right ventricle with no evidence of contraction. The right atrioventricular valve is bicuspid instead of tricuspid.

Rabbits are hind gut fermenters with a large and complex digestive system. They practice cecotrophy, which is the ingestion of mucous-coated night feces. Cecotrophy occurs daily, and it is a method of recycling nutrients such as B vitamins and proteins. It is controlled by the adrenal glands, and therefore may be altered during periods of excessive stress. Rabbits possess abundant gut associated lymphoid tissue located in the Peyer’s patches, lymphoid appendix and sacculus rotundus. These structures comprise nearly 50% of the total mass of lymphoid tissue in the body. Autolysis of these tissues is rapid after death.

Rabbits have alkaline urine with dull yellow to brown calcium carbonate and triple phosphate crystals. Calcium and magnesium are excreted primarily via the urine. Urine may be pigmented dark red to orange which is an incidental finding and may indicate increased ingestion of dietary porphyrins or elevated urobilin.

Female rabbits are does; males are bucks. Bucks reach puberty at 6-10 months of age and does reach puberty at 4-9 months. The breeding lifespan of a doe is 3-4 years. The uterus has two horns and two separate cervices and placentation is hemochorial. Does are induced ovulators. Gestation lasts 25-29 days and does give birth to 4-10 kits. Following parturition, the kits nurse 1-2 times daily. The doe’s milk is high in fat and protein and kits are weaned at 4-6 weeks of age.

Ear vessels are prominent and are readily accessible for blood collection. In the rabbit, the erythrocyte measures 6.5-7.5 μm in diameter. Polychromasia is a normal finding. Reticulocytes make up 2-5% of the red blood cell count and the life span of the red blood cell is 50 days. Heterophils are the counterpart of the neutrophil and measure 9-15 μm and have distinct acidophilic granules. Eosinophils are 12-16 μm and have large cytoplasmic granules that stain dull pink-orange with conventional hematology stains. Lymphocytes are the predominant leukocyte in circulation. Small lymphocytes measure 7-10 μm and large lymphocytes are 10-15 μm. Lymphocytes normally contain a few azurophilic cytoplasmic granules. Basophils may be numerous and represent up to 30% of the circulating leukocyte population.

VIRAL DISEASES

1. Myxomatosis

Myxomatosis is caused by a leporipoxvirus that is endemic in the wild rabbit population. There are two subtypes of the virus: the South American type that is found in *Sylvilagus brasiliensis* (forest rabbits) and the Californian subtype found in brush rabbits.
(S. bachmani). Myxoma virus is transmitted by direct or indirect contact and arthropod vectors such as ticks and fleas also play a role. In the two wild reservoir species, only a localized cutaneous fibroma is produced without systemic disease. However, the disease course is much different in domestic rabbit species. After infection, a primary subcutaneous myxoid mass develops within 3-4 days. At 6-8 days, mucopurulent conjunctivitis, subcutaneous edema and multiple subcutaneous masses develop and scrotal edema and swelling may be prominent in bucks. Clinically, there is moderate leukopenia with significant lymphopenia with a decrease in CD4+ and CD8+ lymphocytes and fever. In peracute cases, rabbits die suddenly with only conjunctival erythema, but the usual time to death is between 8 and 12 days following infection. At autopsy, there is the swelling and edema as previous described along with lymphadenopathy and petechial or larger hemorrhages on the serosal and visceral surfaces of multiple organs. The high mortality rates are the result of multiorgan dysfunction with secondary bacterial infections due to immunosuppression by the virus. Histologically, there is proliferation of large, stellate mesenchymal cells, myxoma cells, interspersed in a mucinous, homogenous matrix with few inflammatory cells. There is also hypertrophy and proliferation of endothelial cells and the overlying epidermis ranges from hyperplastic to degenerative and intracytoplasmic inclusion bodies are often present. Due to viral replication in the lymphoid tissue, there is massive loss of lymphocytes from both the cortical and paracortical areas due to bystander apoptosis. Ability to clear the virus is heavily dependent on cell mediated immunity and neutralizing antibody. There are vaccines available, one uses live Shope fibroma virus and the other has a platform based on attenuated myxoma virus.

2. **Shope Fibroma**
   
   **Shope fibroma** is also caused by a leporipoxvirus that is transmitted by fleas and ticks. Like myxoma virus, the genetic sequence for this virus has also been determined. Shope fibroma virus is the first mammalian virus potentially capable of photoreactivating ultraviolet DNA damage due to its ability to encode a type II DNA photolyase. The Eastern cottontail rabbit is the natural host, but other species of rabbits are susceptible as well. The virus produces firm flattened subcutaneous, freely moveable, up to 7 cm diameter masses primarily on the legs and feet, and less commonly on the muzzle and in the periorbital and perineal areas that occur most commonly in the fall. In newborn and immunocompromised adults, Shope fibroma virus can cause a fatal disseminated disease similar to myxomatosis. Histologically, there is localized fibroblastic proliferation with infiltration by low to moderate numbers of mononuclear and polymorphonuclear cells. Fibroblasts are fusiform to polygonal and contain intracytoplasmic eosinophilic viral inclusion bodies. There is a single report of a cataract in a rabbit. The diagnosis was based on signalment, clinical signs, histologic appearance and virus isolation.

3. **Papillomaviruses**
   
   **Cutaneous papillomatosis** is typically a benign disease affecting only the haired skin of cottontails caused by a papilloma virus that is mechanically transmitted through insect vectors. The natural host is the cottontail rabbit. Clinically, the lesions are cornified, pedunculated masses with fleshy central areas. Histologically, these lesions have the typical appearance of a typical squamous papilloma with masses lined by stratified squamous epithelial cells with cores of fibrous connective tissue, parakeratotic hyperkeratosis and viral inclusion bodies. A case report detailed the finding of virus in Langerhans cells which has not been reported before. In cottontails, the papillomas typically regress, but in domestic rabbits the papillomas may progress to squamous cell
carcinomas. Regression is dependent on the host genetic makeup as well as the genetic variability of the virus. Papillomatosis has been studied in rabbits to learn more about the prevention of malignant progression of human papillomavirus-associated lesions in humans.

**Oral papillomatosis** is caused by a papillomavirus and usually occurs in young rabbits, 2-18 months of age. The condition is characterized by the presence of white, fleshy papillomatous masses along the ventral aspect of the tongue. The virus is spread by direct contact in areas where there has been injury to the oral mucosa. Rough or hard food, chewing on rough cage bars and or malocclusion may predispose animals to infection. The histologic appearance is a typical squamous papilloma with basophilic intranuclear inclusions in epithelial cells. A recent report documented a persistent papilloma in the conjunctiva in a Flemish Giant pet rabbit that was caused by an oral papilloma virus strain.

### 4. Rabbitpox virus

**Rabbit pox** is caused by an orthopoxvirus that has significant homology with the vaccinia virus. The natural route of infection is by aerosol followed by viremia with viral replication in the lymphoid tissue with systemic spread. Clinically, rabbits are febrile with weight loss followed by ocular discharge and dyspnea. Papular lesions occur in the oropharynx, respiratory tract, skin, mucocutaneous sites, spleen, lymph nodes and liver and are characterized by focal necrosis with leukocyte infiltration. Rabbitpox virus is proposed as an animal model for human smallpox.

### 5. Rabbit herpesviruses

**Leporid herpesvirus 3 (Herpesvirus sylvilagus)** is a gamma herpesvirus found in wild cottontail rabbits; domestic rabbits are not affected. Juveniles are affected to a greater degree than adults. There is prominent lymphoproliferative disease in lymph nodes, spleen, kidney and liver.

There is a report of a novel alpha herpes virus, now classified as **leporid herpesvirus 4**, causing an outbreak of disease in rabbits in Alaska. Affected rabbits had many lesions similar to myxomatosis including necrosis of ocular and anogenital skin and lymphoid necrosis, but with vasculitis, intranuclear viral inclusions and syncytial cells. An individual case was reported from Canada in a pet New Zealand white rabbit. Similar to the report from Alaska, there was necrosis, vasculitis and intranuclear viral inclusion bodies in the lung, spleen, ileum and skin.

Rabbits are very sensitive to infection with **herpes simplex virus**. Affected rabbits exhibit typical neurologic signs and anorexia and weakness. There is nonsuppurative, necrotizing meningoencephalitis with amphophilic intranuclear inclusion bodies in neurons and astroglial cells. This is a zoonotic disease and cases in rabbits have been traced back to herpetic lesions in humans. The rabbit is a major animal model for studying herpes simplex virus 1 latency and shedding, especially in the eyes.

Rabbits are also animal models for malignant catarrhal fever, pseudorabies and bovine herpesvirus type 5.

### 6. Rabbit coronavirus

Pleural effusion and cardiomyopathy due to **coronavirus** occurs in laboratory rabbits. This virus is antigenically related to human coronavirus strain 229E and it has been suggested that the rabbit virus is a human contaminant. Transmission is through direct contact and there are carrier animals. Gross lesions of pleural effusion disease include pleural effusion, pulmonary edema, right-sided cardiac dilatation, peritoneal...
effusion, mesenteric lymphadenopathy, necrosis of the liver, kidney and lung, iridocyclitis, and lymphoid depletion. Histologically, there is lymphoid depletion of splenic follicles, focal degenerative changes in the thymus and lymph nodes, proliferative changes in glomerular tufts, and uveitis. In the cardiomyopathy form, there is focal to diffuse myocardial degeneration and necrosis, pulmonary edema, lymphoid depletion to hyperplasia, and diaphragmatic muscular degeneration and necrosis. The differential diagnosis for myocardial necrosis in rabbits is hypovitaminosis E, salmonellosis, Tyzzer’s disease, pasteurellosis, encephalitozoonosis, and detomidine-containing anesthetic agents.

**Coronavirus** can cause enteritis in young rabbits, 3-8 weeks of age. Clinically, the affected rabbits are thin and dehydrated with fecal staining in the perineal region. The cecum is distended and filled with watery, beige to tan fecal material. The histological appearance is similar to rotavirus with necrosis of villous epithelial cells and M-cell necrosis. Diagnosis is by finding typical viral particles in feces by electron microscopy.

7. **Rabbit rotavirus**

**Lapine rotavirus (group A)** causes mild to severe diarrhea with high morbidity in suckling and weanling rabbits. The virus is transmitted by direct contact by ingestion and is endemic in many rabbitries. It can be found in normal rabbits free of disease and antibody titers in normal rabbits may also be present. Clinically, the rabbit is dehydrated and the cecum is distended, congested and filled with fluid contents. Histologically, in the small intestine there is villar atrophy, blunting, and fusion with vacuolation and flattening of apical enterocytes. In the cecum, there are focal areas of desquamation with basophilic debris in the cytoplasm of affected enterocytes. Diarrhea is more severe with coinfections such as those with *E. coli*. As this virus is prevalent, regular and stringent screening of colonies is highly recommended. There is a recent report (*Vet Micro*) of a colony that was infected with a bovine rotavirus strain.

8. **Rabbit viral hemorrhagic disease virus**

**Rabbit viral hemorrhagic disease (RVHD)** is caused by a Lagovirus in the family *Caliciviridae* and is considered a foreign animal disease. Other viruses in the *Lagovirus* genus include European Brown Hare Syndrome Virus and Rabbit Calicivirus. This is the only reportable disease in rabbits in the U.S. To date, there have been four separate outbreaks in the U.S. and the virus sequences show similarity to genomes from China. RVHD is a peracute disease of adult rabbits that results in hepatic, enteric, and lymphoid necrosis. The virus is transmitted by direct contact and by contaminated fomites. Carrier states are present and the virus is shed in the urine for up to 4 weeks and long term fecal shedding may be possible. This virus has a predilection for hepatocytes and macrophages, where it replicates. The clinical signs vary but include sudden death, fever, depression, CNS signs, and serosanguinous discharge. Some animals will have a more subacute course of diseases, dying 1-2 weeks after infection. Necropsy findings include hepatomegaly, splenomegaly, and hemorrhage and serosal ecchymoses. Histologically, there is hepatic necrosis that begins in the periportal areas and spreads to the entire lobule. There is also heterophilic infiltration, crypt necrosis, pulmonary edema, hemorrhage, and lymphocytolysis. There are fibrin thrombi in the small caliber vessels throughout the body. In an outbreak in Illinois, clinical signs included depression, anorexia, fever, paddling, convulsions and sudden death. Diagnosis was made by hemagglutination assay and viral antigen-detection ELISA.
There are now reports of RVHD variants including a recent report (Emerging Infect Dis, Vol.18, No. 12) from Spain where kits and rabbits less than 30 days old were affected with greater than 50% mortality.

9. **Novel Rabbit Calicivirus**

There was an outbreak of acute viral disease in a rabbitry of New Zealand white rabbits that clinically exhibited vulvar hemorrhage (does), epistaxis, ataxia, opisthotonos, diarrhea, ocular discharge, vocalization and death. Gross necropsy lesions included conjunctival congestion, cyanosis of the lips and ear tips, friable, tan livers with an accentuated lobular pattern, gastric petechiae and colonic mucosal hemorrhage. Histologically, there was random or periportal hepatic necrosis and hemorrhages. A virus was isolated with 79% similarity with the RVHD virus but the investigators could not induce experimental disease.

9. **Rabies Virus**

Rabbits are susceptible to infection with rabies virus. All reports have been in states with enzootic raccoon-variant rabies virus. Affected rabbits were housed outdoors with potential or reported contact with wildlife. The clinical disease is the paralytic form and affected rabbits die within 3 to 4 days. Diagnosis is by immunofluorescent testing of brain tissue. Prevention is through double caging of outdoor housed rabbits and prohibition of free-roaming while outdoors.

**REFERENCES FOR VIRAL DISEASES:**


Eidson, M; et al: Rabies virus infection in a pet guinea pig and seven pet rabbits. JAVMA, Vol 227, No. 6, Sep 15, 2005, pp. 932-935.


BACTERIAL DISEASES

1. **Pasteurella multocida**
   
   Pasteuriosis is probably the most significant disease of rabbits. In conventional rabbit colonies, the incidence of infection may be high. Close to 50% and up to 70% of the animals may harbor the organism in the upper respiratory tract and tympanic bullae. *P. multocida* is a Gram negative, bipolar staining bacillus that is transmitted through direct contact from animals shedding the organism from nasal and/or vaginal secretions. Most infections are due to serogroup A and to a lesser extent, serogroup D, but new evidence shows that serogroup F also causes disease in rabbits. Nursing rabbits can become infected within the first week of life from nursing carrier does. Aerosols do not appear to be an important means of spread and using a modified barrier system can prevent infection. Fomites may be involved in transmission; however, a large number of organisms are required for infection. Interspecies transmission has been experimentally reproduced. There seems to be a seasonal influence with infection because most problems occur in the spring and fall. Predisposing factors include increased atmospheric ammonia concentration, pregnancy, concomitant disease, environmental disturbances and experimental manipulation.

   *P. multocida* causes a wide range of clinical disease in rabbits including rhinitis, pneumonia, otitis media, meningoencephalitis, abscessation, mastitis, dermatitis and septicemia. Some of the gross lesions associated with infection of the respiratory tract by *P. multocida* are catarrhal to mucopurulent rhinitis, atrophic rhinitis, chronic pneumonia characterized by localized consolidation of the anteroventral lobes with atelectasis, acute fibrinous pneumonia with fibrinothrombotic lobar pneumonia and pleuritis with possible pericarditis and/or pyothorax, and pulmonary abscesses.

   Histologically, the pneumonia may be characterized by chronic bronchitis with peribronchial lymphocytic infiltration to alveolitis with primarily heterophilic inflammation. In the acute necrotizing form, there is destruction of alveoli and small airways, alveolar flooding with fibrinous exudate and erythrocytes and infiltration by large numbers of heterophils. Multinucleate giant cells may be present in affected alveoli. Other bacteria that cause similar lesions in the lung of rabbits are *Bordatella bronchiseptica*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. The diagnosis should be confirmed with bacterial culture. For control of this important disease, infected rabbits should be culled and barrier housing with adequate ventilation should be used.

   *P. multocida* infections outside of the respiratory tract are characterized by necrosis, large numbers of heterophils and bacteria.

2. **Bordatella bronchiseptica** is often present together with *Pasteurella multocida*. Its role as a definitive cause of disease in the respiratory tract of rabbits has not yet been firmly established. The organism can be recovered from the upper and lower respiratory tract of healthy rabbits. It is transmitted by direct contact through aerosols. Suppurative bronchopneumonia can be produced experimentally by treating rabbits with corticosteroids, then infecting them. However, *B. bronchiseptica* has been isolated from
natural cases of localized pneumonia. Histologically, there is a chronic interstitial pneumonia, chronic bronchiolitis and perivascular and peribronchial accumulations of lymphocytes, plasma cells, and macrophages.

3. **Staphylococcus aureus**

Strains of varying pathogenicity of this Gram positive bacterium can cause clinical disease in limited individuals, or produce colony problems. A recent study showed that colonization capacity is an important virulence determinant in rabbit staphylococcosis. The most common clinical lesions in rabbits due to *S. aureus* are subcutaneous abscesses, pododermatitis, mastitis and septicemia. The organism is transmitted by direct contact via aerosol. Like *P. multocida*, carrier animals can harbor the bacterium in the upper respiratory tract. Umbilical vessels and skin abrasions are two other possible entry sites. After inoculation, *Staphylococcus* can spread hematogenously or via local extension.

**Ulcerative pododermatitis** or “sore hock” is a common problem. Overweight males housed on wire-floor cages are predisposed to sorehock. Poor sanitation is another predisposing factor. Clinically, there are ulcerative skin lesions on the plantar surface of the metatarsal and/or metacarpal regions. Histologically, there is epidermal hyperplasia with ulceration and/or erosion covered by a serocellular crust with a mixed inflammatory cell infiltrate in the dermis. Diagnosis is made by demonstration of Gram positive cocci in section and by positive bacterial culture.

**Bacterial mastitis** has been attributed to the following organisms: *Staphylococcus* sp., *Pasteurella multocida*, and *Streptococcus* sp. In lay terms, it is called “blue breast” and occurs most commonly in recently kindled and heavily lactating does. The disease can range from a peracute to acute gangrenous form that is rapidly fatal to subacute to chronic. Orphan young can spread disease to an unaffected doe and infection can spread to multiple mammary glands. Clinically, the skin overlying the mammary glands has a red to dark blue discoloration and the gland contains serous to purulent exudate. Nursing young may develop an acute fatal septicemia. Histologically, the lesions are suppurative with necrosis and variable amounts of fibrous connective tissue (depending on the chronicity) and bacteria are often present.

**Pneumonia** caused by *S. aureus* is often very suppurative and is composed of large amounts of white purulent material. Histologically, there are focal suppurative necrotizing lesions with colonies of coci. The bacteria are often present in section, but infections should always be confirmed with bacterial culture.

**Septicemia** usually occurs in the very young and sporadically in adults. There are suppurative lesions disseminated throughout the body, especially in the lung, kidney, spleen and heart.

4. **Treponema paraluiscuniculi**

**Treponematosis** is common in wild rabbits and is often referred to as rabbit syphilis or vent disease. The disease is transmitted venereally, although transmission through extragenital contact can occur and the organism is able to penetrate intact mucous membranes. Susceptibility is age and breed dependent and the disease is generally self-limiting. *Treponema paraluiscuniculi* is a 5-20 μm, Gram negative helical bacillus with tight or irregular spirals. Clinically, there is edema and erythema at the mucocutaneous junctions of the vulva, prepuce, anal region, muzzle, and periorbital area. Lesions are often crusty. Popliteal and inguinal lymph nodes may be enlarged. The histologic changes are confined to the epithelium and superficial dermis and are characterized by epidermal hyperplasia, epidermal cell necrosis, erosions, and ulcerations with infiltration by predominantly plasma cells and lymphocytes. The
5. **Pseudomonas aeruginosa**  
*Pseudomonas aeruginosa* causes a moist dermatitis with a characteristic green color.

6. **Arcanobacter pyogenes**  
*Arcanobacter* (Corynebacterium) *pyogenes* causes suppurative and ulcerative dermatitis in rabbits.

7. **Fusobacterium necrophorum** has been reported to cause suppurative and ulcerative dermatitis.

8. **Clostridiosis** in rabbits has been attributed to infection with *Clostridium perfringens*, *C. difficile*, and *C. spiroforme*. *C. spiroforme* produces a type E iota toxin and is the most common of the clostridial bacteria associated with enteritis complex in juvenile rabbits. Infections in rabbitries are common and at necropsy of diarrheic rabbits, it is isolated from over 50% of the cases, and in one study, 90% of these strains were toxigenic. Concurrent infections (*E. coli*, *Eimeria* sp, *Cryptosporidia*, and rotavirus) can also allow colonization and proliferation of clostridial bacteria with subsequent toxin production. There are different clinical forms of the condition. In the peracute form, there is death with little or no premonitory signs. In the chronic condition, there is anorexia, wasting and intermittent diarrhea over several days. At necropsy, the body is in good nutritional condition and there is soiling of the perineal region with watery green to tarry brown feces. There is often a straw colored peritoneal effusion, ecchymoses on the cecal serosa, with occasional involvement of the distal ileum and proximal colon. There may be epicardial and thymic ecchymoses. The cecum and adjacent areas are frequently dilated and are filled with watery to mucoid, green to dark brown material and gas. Hemorrhage and ulceration and/or fibrin may markedly thicken these areas. Histologically, there is necrotizing typhlocolitis with effacement of the mucosal architecture, loss of epithelium, ulceration, fibrinous exudation, congestion, hemorrhage, and infiltration by primarily heterophils. Thrombi may be present on the mucosal surface. The diagnosis can be confirmed by anaerobic bacterial culture and the toxins can be identified. *C. perfringens* causes an enterotoxemia-like condition in young rabbits that result in cecal hemorrhage and edema. *C. difficile* causes disease in rabbits after antibiotic administration and/or dietary change. In contrast to other species, lesions in rabbits due to *C. difficile* most commonly affect the ileum and not the colon as in other species.

9. **Clostridium piliforme** is the causative agent of Tyzzer's disease and is a Gram negative, motile, filamentous, spore forming bacillus. Predisposing factors are important in this condition and include poor sanitation, stress and sulfonamide therapy. Many other species of laboratory and domestic animals are also infected; therefore interspecies transmission must be prevented. Survivors can become chronically infected and serve as carriers and clinical disease can be provoked by the administration of corticosteroids. *C. piliforme* is transmitted by direct contact through ingestion and the organism can survive in soiled bedding for up to one year. The bacterium causes an acute disease characterized by a sudden outbreak of profuse, watery diarrhea with a short course and...
high mortality rate. At necropsy, there is a classic triad of lesions that include segmental necrosis, edema and hemorrhage of the small and large intestine; multifocal hepatic necrosis, and myocardial necrosis. Histologically, there is necrosis, edema, and hemorrhage with intracellular bacterial present in enterocytes, hepatocytes and cardiomyocytes. The bacilli can be readily demonstrated with Giemsa, PAS, and silver stains. Colony surveillance is done through serology; any positive results should be followed-up with PCR and/or histopathology.

10. **E. coli**
The attaching and effacing (enteropathogenic) strains cause colibacillosis in rabbits and are a major cause of enteritis in commercial rabbitries and rabbits are used as an animal model to study enteropathogenic *E. coli* (EPEC). The organism is not normally present or is present in small numbers within the gastrointestinal tract of suckling and weanling rabbits. There is a rapid proliferation of these bacteria with a change in intestinal pH due to such things as intestinal coccidiosis and diets that require a high HCl concentration for digestion, such as high carbohydrate diets. Some strains affect only suckling rabbits and attach to the full length of the small and large intestine, while other strains affect weanlings only and attach only to the ileum and large intestine. The organism attaches to the Peyer’s patch dome epithelium and then later colonizes and attaches to enterocytes. At necropsy, the body is dehydrated, there is perineal staining with watery, yellow to brown fecal material, the cecum is distended with watery yellow to gray-brown contents and there may be serosal ecchymoses, edema in the cecal and colonic walls and enlarged mesenteric lymph nodes. The small intestine is usually grossly normal. Histologically, changes are most severe and extensive in weanling rabbits. Ileal villi are blunted with edema and heterophilic infiltration of the lamina propria. The enterocytes at the villar tips are swollen with attached bacilli.

Dutch Belted rabbits either naturally or experimentally infected with enterohemorrhagic strains of *E. coli* develop bloody diarrhea with typhlocolitis with nephropathy consistent with the hemolytic-uremic syndrome and may be a possible animal model for this infectious disease.

11. **Lawsonia intracellularis** is a curved, obligate intracellular Gram negative bacillus that causes proliferative enteropathy not only in rabbits, but in many other species. The organism produces diarrhea in suckling, weanling, and adult rabbits acutely and can also cause subclinical disease. The disease in rabbits is similar to that in hamsters and pigs. At necropsy, there are semi-fluid, mucinous contents in a thickened colonic and rectal mucosa. Histologically, there is variable involvement in the terminal small intestine, cecum, and colon. Lesions vary from erosive and suppurative to proliferative. In the erosive form, there is focal to segmental loss of enterocytes with heterophilic infiltration. The proliferative form is characterized by multifocal to diffuse enterocyte hyperplasia and hyperplasia of crypt and villar epithelium with infiltration by variable numbers of lymphocytes, heterophils, macrophages and occasionally, multinucleate giant cell macrophages. Bacteria can be demonstrated within enterocytes with silver stains. By electron microscopy, curved, bacillus-like organisms are present within the cytoplasm at the luminal edge of the epithelium.

12. **Salmonella typhimurium** and **S. enteriditis** are Gram negative bacilli that can cause rare infections in rabbits that result in septicemia, diarrhea, abortions and death. These bacteria are transmitted by the fecal-oral route and cause polyserositis, focal hepatic necrosis, splenomegaly, enteritis with fibrinous exudate, necrotizing myocarditis and suppurative metritis.
13. **Yersinosis** due to *Yersinia pseudotuberculosis* or *Y. enterocolitica* is an important disease of the European brown hare and occurs rarely in domestic rabbits and is an acute to chronic infection. The organism is transmitted by ingestion of contaminated food and water. Wild rodents and birds are carriers. The clinical signs are nonspecific and include poor condition and weight loss. Histologically there is necrosis in the liver, spleen, cecum, and lymph nodes and occasionally, the reproductive tract may be affected. There are large numbers of coccobacilli within necrotic areas.

14. **Francisella tularensis**, the causative agent of Tularemia or “Rabbit Fever” is a Gram negative bacillus. Tularemia is an important zoonotic disease and the causative bacterium is a potential biowarfare agent. The bacterium is transmitted through direct contact and through insect vectors. Ticks (*Amblyoma americanum* and *Dermacentor variabilis*) appear to be the most important vector, but other vectors such as mosquitoes, sucking lice and biting lice are also capable of transmitting the agent. The disease is widespread in Eastern cottontail rabbits in the U.S., but is limited to the snowshoe hare in Canada. Rabbits are usually found dead. Death usually occurs in 8-14 days after infection. There is necrosis of the spleen, liver and lymph nodes with colonies of bacilli.

15. **Listeria monocytogenes** is a Gram positive coccobacillus transmitted through ingestion of contaminated feed and/or water and transplacentally that causes hepatic necrosis and nonsuppurative meningoencephalitis in rabbits. It also causes fever, abortions and sudden death in does in late gestation. Infected newborn kits may develop systemic disease, may have stunted growth and/or develop meningoencephalitis.

16. **Cilia-associated respiratory (CAR) bacillus** is a Gram negative, 6-8 μm motile, non-spore forming bacillus that causes generally subclinical infections in rabbits. CAR bacillus isolates that infect mice and rats are host specific and do not infect rabbits. The organism colonizes the ciliated epithelial cells lining the larynx, trachea, and bronchi. Histologically, there may be a chronic tracheitis with goblet cell hyperplasia. The organism can be demonstrated in section with silver stain.

17. **Mycobacteriosis**

   Natural infections are rare in rabbits. *Mycobacterium bovis*, *M. avium*, and *M. tuberculosis* infections have been rarely reported. There is a single report of *M. genevense* infection in a dwarf rabbit that resulted in granulomatous pneumonia. Rabbits are animal models for tuberculosis and appear to a particularly good model for latent tuberculosis.

**REFERENCES FOR BACTERIAL DISEASES:**


MYCOTIC DISEASES

1. **Ringworm** caused by *Trichophyton mentagrophytes, Microsporum canis* and *M. gypseum* is the most common fungal disease in rabbits. Rabbits may serve as inapparent carriers and they can transmit infection to other animals, as well as humans. The young and immunocompromised are most susceptible. Clinically, lesions are most commonly present on the head and ears and are raised, circumscribed, and erythematous. Histologically, there is hyperkeratosis, epidermal hyperplasia, folliculitis, and arthrospores. Diagnosis is by skin scrapings cleared in 10% potassium hydroxide solution. In tissue sections, the arthrospores are stained with methenamine silver and periodic acid Schiff stains.

2. **Aspergillus fumigatus** and *A. flavus* is occasionally found at necropsy, almost exclusively in wild rabbits. It can result in disseminated lesions in the liver, kidney, brain, lung, heart, intestine and spleen. The lesions are circumscribed nodules with a central area of necrosis surrounded by neutrophils, lymphocytes, plasma cells, macrophages, and multinucleate giant cells. Fungal hyphae can be demonstrated with silver or PAS stains.

MYCOTIC DISEASE REFERENCES


PROTOZAL/MICROSPORIDIAL DISEASES

1. **Encephalitozoon cuniculi**  
*Encephalitozoon cuniculi* is an oval, 1 x 2 μm Gram positive, obligate intracellular microsporidian parasite that is widespread in domestic rabbits and is probably the most common spontaneous microsporidian infection in animals and is also considered a zoonotic disease. Infection in rabbits is usually subclinical, but can cause nervous system disease and death in heavy infections. Dwarf rabbits are highly susceptible to infection and development of disseminated disease. Three major types of clinical disease can occur: a neurological form, an ocular form and a renal form. Clinical signs of the neurologic form include head tilt, seizures, ataxia, paralysis and muscular weakness and usually occur approximately 30 days after infection. The ocular form is associated with cataracts and extensive damage to the lens with uveitis. Natural transmission is by ingestion of spore-contaminated urine and transplacental transmission also occurs from pregnant does to their kits. Spores can survive in the environment for at least 4 weeks at room temperature. Spores are spread hematogenously within the cytoplasm of macrophages. The spores selectively parasitize vascular endothelium, especially in the brain and kidney, as well as renal tubular
epithelium. Then the spores localize in the liver, lung, adrenal gland, spleen and other highly vascular organs. Within the cell, the spores are contained within a parasitophorous vacuole or pseudocyst and are called trophozoites or schizonts that multiply by ordinary fission or schizogony. When the trophozoites mature, they become sporonts, then sporoblasts, and then eventually spores. The organism has a polar filament that it uses to penetrate host cell membranes to inject sporoplasm into the host cell.

Antemortem diagnosis is difficult, since there is a high prevalence of seropositivity across different colonies. A recent paper described the use of cerebrospinal fluid (CSF) coupled with clinical signs to arrive at a preliminary diagnosis. Affected rabbits had a lymphomonocytic pleocytosis and elevated protein levels in the CSF. Only 20% of rabbits have detectable spores in the urine. PCR was used in one study to detect organisms in samples of liquefied lens material.

Definitive diagnosis is by histopathology. There are no gross lesions in the CNS, but histologically, there is focal, nodular, nonsuppurative to granulomatous meningoencephalitis with astroglialosis and perivascular lymphocytic cuffs. In ocular lesions, there is usually a granulomatous response and rupture of the lens capsule. Gross lesions of the kidney include focal, irregular, depressed pale areas, 2-4 mm diameter on the cortical surface. Histologically, there is focal to segmental, granulomatous to chronic interstitial nephritis with tubular ectasia, and spores within tubular epithelial cells, macrophages, and in areas of inflammation. Spores can be demonstrated with Gram, Giemsa, and carbol fuchsin stains. Immunohistochemistry can be used to identify the spores.

Albendazole, fenbendazole and anti-inflammatory drugs in addition to supportive care have been used to treat encephalitozoonosis.

2. *Toxoplasma gondii*

This protozoan rarely causes clinical disease in laboratory rabbits. In a recent study, brown hares and rabbits were experimentally infected with *Toxoplasma gondii*. The hares had fatal, disseminated disease, while the rabbits had mostly subclinical disease. The typical findings included enteritis, mesenteric lymphadenitis, splenomegaly and necrotizing hepatitis. Histologically, there is necrosis with tachyzoites and/or protozoal cysts. The principal differential diagnosis is *Encephalitozoon cuniculi*.

3. **Coccidiosis**

**Intestinal coccidiosis** is caused by numerous species in the genus *Eimeria*. The species considered to be most pathogenic in rabbits are *magna*, *intestinalis* and *flavescens*, *Irresidua*, and *piriformis* are considered to be intermediately pathogenic. Least pathogenic species include *perforans*, *neoleporis* and *media*. Coccidiosis is a common, widespread problem in commercial operations and research facilities. Coccidia may act as copathogens in other conditions and as with many of the conditions of the gastrointestinal tract in rabbits, changes in environment and management may predispose to infection. Coccidia are transmitted through fecal-oral contact and infections with more than one species is not uncommon. After passage in the feces, the oocysts require one or more days to sporulate. After the sporulated oocysts are ingested, sporozoites are released and then invade enterocytes and multiply by schizogony. One or more sexual cycles take place, then gametogony occurs and oocysts are formed and passed in the feces. Clinical disease occurs most frequently in weanlings. The sexual stage causes the most damage and results in extensive destruction of enterocytes and other cells within the lamina propria. Gross lesions include dark green to brown watery foul smelling exudate in the cecum and colon with
edema and congestion of the mucosa. Where the lesion is located depends on the species involved. Histologically, there is destruction and necrosis of enterocytes, villar atrophy, marked heterophilic infiltration and presence of gametocytes and oocytes. The disease can be diagnosed by fecal flotation or by mucosal scrapings. Bacterial culture should also be performed, as there are often co-infections.

**Hepatic coccidiosis** occurs in both wild and domestic rabbits and is due to infection with *Eimeria stiedae*. Weanlings are most often affected; older rabbits develop immunity. The organism is transmitted through the ingestion of sporulated oocysts. After ingestion, the sporozoites penetrate the intestinal epithelium and are then transported to the liver, where they invade biliary epithelial cells and undergo schizogony. After gametogony, oocysts are released into bile ducts, pass to the intestinal tract via the bile and are then passed into the feces. Clinically, infections are often inapparent. However, anorexia, debilitation, constipation or diarrhea may be present in heavy infections. Other clinical signs may include enlarged liver, pendulous abdomen, and icterus. Liver enzymes and serum bilirubin may be elevated. At necropsy, there is hepatomegaly with multifocal, raised yellow to pearl gray, circumscribed foci that contain inspissated dark green to tan material. The gallbladder mucosa is thickened and filled with viscid green bile and debris. Histologically, there is bile duct hyperplasia with ectasia and papillary projections covered by reactive epithelial cells and gametocytes and oocysts. Periportal fibrosis and mixed inflammatory cell infiltrate may also be present. Oocysts are present in gallbladder aspirates or impression smears. Histopathology is pathognomonic.

4. **Cryptosporidiosis** due to *Cryptosporidium parvum* and *C. cuniculus* is a rare primary cause of enteritis in young rabbits. It is usually identified as an incidental finding and causes villous blunting, a decrease in crypt-villous ratio, and edema.

**PROTOZOAL DISEASE REFERENCES**

PARASITIC DISEASES

1. **Psoroptes cuniculi**
   This is the ear mite of rabbits and is the most common and costliest ectoparasite infection of rabbits. Ear mites are transmitted by direct contact and spend their entire life span in the external ear. Mites can survive off the host in the crust material for up to 21 days. Severely affected ears may contain as many as 10,000 mites. The mites are nonburrowing and chew and pierce the epidermis of the external ear. This activity incites an inflammatory response that is similar to an IgE mediated type I hypersensitivity reaction. The clinical appearance is the presence of light brown, thick, crusty, foul smelling exudate in the external ear canal and pinnae. The skin beneath the crusts is alopecic and erythematous. Self-excoriation can lead to secondary bacterial infections. Histologically there is hyperkeratosis, heterophils, macrophages, eosinophils, parasites, and eggs. The mites are easily demonstrated on swabs. A recent study documented that moxidectin, an equine dewormer, was a safe and effective treatment for psoroptic mange in rabbits. Another paper found selamectin at a dose of 6-18 mg/kg was shown to eliminate mites from rabbits naturally infested with *P. cuniculi*.

2. Fur mites, *Cheyletiella parasitovorax*, can cause mild alopecia without pruritis or no clinical signs. These mites are transmitted by direct contact and the entire life cycle is spent on the rabbit. Clinically, there is alopecia, scaliness and crusts, especially over the dorsal trunk and scapular areas. Histologically, there is mild hyperkeratosis with mononuclear cell infiltration. The diagnosis is confirmed by finding the mites in skin scrapings.

3. Sarcoptic mange due to *Sarcoptes scabei* and *S. cuniculi* causes alopecia and dermatitis involving the face, nose, lips, and external genitalia. The mites burrow through and inhabit the epidermis causing irritation and producing a hypersensitivity reaction with inflammation. There is parakeratotic hyperkeratosis, acanthosis, lymphoplasmacytic and eosinophilic inflammation and cross-sections of mites, eggs and mite pigment. Selamectin, a novel ivermectin, can be used at a dose of 6-18 mg/kg to treat sarcoptic mange in the rabbit.

4. The pinworm of rabbits is *Passalurus ambiguus*. It is fairly common in rabbitries and causes occasional diarrhea. The parasite is transmitted through the fecal-oral route. Adult worms are present in the cecum and colon and larvae are present on the mucosa of the small intestine and cecum. Diagnosis is made by fecal flotation. Eggs are morulated and are slightly flattened on one side. Most cases are asymptomatic, but impaired weight gain, poor breeding and death have been reported with heavy infections.

5. Cestodes
   Rabbits are the intermediate hosts for *Taenia serialis* and *Taenia pisiformis*. Both *T. serialis* and *T. pisiformis* can produce lesions in the subcutaneous tissues and/or mesentery as well as the liver. The Laboratory Animal Resources area at Colorado State University reported three cases within a daily census of 250 rabbits over 10 years, a <1% incidence. There is a single report of *Taenia serialis* causing exophthalmos in a rabbit. It presented as a soft tissue swelling within the orbit of the right eye. Surgery was
performed and a large cystic structure was removed. Histopathology revealed the cyst was a coenurus of *Taenia serialis*.

6. **Obeliscoides cuniculi**

*Obeliscoides cuniculi* is a trichostrongyle found in the stomach of rabbits that graze fresh grass or are fed fresh grass as feed. Most infections are asymptomatic, but in heavy infections anorexia, lethargy and weight loss may be seen. Treatment is ivermectin injected subcutaneously and then repeated 2 weeks later.

7. **Baylisascaris procyonis**

The larval stages of the raccoon roundworm produce necrotizing tracts/lesions mainly in rabbits housed outdoors that have consumed feed contaminated by raccoon feces. Clinically, there is a syndrome of progressive neurological signs including circling, torticollis, tremor and ataxia. Histologically, there are areas of malacia with perivascular cuffing and infiltration by lymphocytes, plasma cells and heterophils. Sections of larvae may be present within the areas of malacia, or in more normal-appearing areas away from the malacia. Digestion of the brain may be necessary to find the larvae. Visceral lesions may be present in the heart, liver, and kidney.

**PARASITIC DISEASE REFERENCES:**


Deeb, BJ and DiGiacomo, RF: Cerebral larval migrans caused by *Baylisascaris* sp. in pet rabbits. JAVMA, Vol. 205, No. 12, pp. 1744-47.


**NUTRITIONAL AND METABOLIC DISEASES**

1. Nutritional problems are rare due to quality control standards in the commercial feed industry. However, problems can arise especially with the use of individually formulated diets. **Vitamin E deficiency** can result in muscular soreness and stiffness. Grossly, there are pale streaks in skeletal and cardiac muscle. Histologically, there is myofiber...
degeneration and necrosis with mineralization and histiocytic inflammation. **Vitamin E deficiency** can cause neonatal mortality and infertility and ocular malformations in kits.

2. Rabbits are very sensitive to levels of **Vitamin D** in the diet. In fact, toxicity can result from levels as little as five times normal. Adults are more sensitive than younger rabbits. Clinical signs are nonspecific and include anorexia, weight loss and infertility. There is increased calcium absorption from the intestine, increased renal tubular resorption and increased resorption from bone. Histologically, there is calcification of the renal tubular epithelium and glomerular and tubular basement membranes, smooth muscle, myocardium, intima and media of larger arterioles and arteries, gastric mucosa, large intestine and lung. In the skeleton, there is osteodystrophy with osteoid dysplasia and osteosclerosis. There is excess production and deposition of an abnormal osteoid that is highly cellular with many active osteoblasts.

3. **Hypo and hypervitaminosis A** produce similar clinical manifestations and include poor conception rates, congenital anomalies, fetal resorption, abortion, and birth of thin, weak kits. Ocular malformations may be present in kits. Administration of Vitamin E can lower levels of Vitamin A in cases of hypervitaminosis A.

4. The Watanabe rabbit has been used extensively as an animal model of natural endogenous **atherosclerosis**. This trait is due to a single-gene defect in the gene that codes for low density lipoprotein (LDL) receptors. These rabbits develop a fulminant hypercholesterolemia in the face of a low cholesterol diet. These rabbits have increased plasma LDL cholesterol concentrations and increased plasma concentrations of apolipoprotein E. These lesions are very similar to those in man, but in rabbits they do not progress to advanced or complicated lesions as in man. However, dietary modifications such as the addition of fats to the diet can produce lesions more similar to those in humans. Atherosclerotic lesions can also be induced experimentally in rabbits by feeding a high cholesterol diet and/or producing arterial injury by balloon catheter. Watanabe rabbits develop subcutaneous xanthomas and there is a report documenting hyperlipidemic ocular lesions affecting the corneoscleral junction and iris.

5. **Carbohydrate overload**, low fiber, high starch diets fed to young animals results in high concentrations of starches in the cecum and colon and a change in pH. This can lead to proliferation of E. coli, Clostridium perfringens, or C. spiroforme. During the fermentation of these starches, toxins are produced that may damage the mucosal surface and cause movement of water and electrolytes into the lumen.

6. **Pregnancy toxemia** occurs in does usually during the last week of pregnancy. Primiparous, obese animals on high planes of nutrition that suddenly go off feed are most at risk. Clinical pathological abnormalities include ketosis, hypocalcemia, hyperphosphatemia and fluctuating blood glucose. At necropsy, there are excessive body fat stores with fatty infiltration of the liver, kidney, and adrenal glands.

7. There is a recent report of osseous proliferations of extremities and mandibles with proliferative gastroduodenopathy in a group of rabbits attributed to **chronic fluorosis** that was traced back to the feed.

**NUTRITIONAL AND METABOLIC DISEASE REFERENCES:**
CONGENITAL DISEASES

1. Mandibular Prognathism (Malocclusion)
   Malocclusion is the most common dental abnormality of rabbits and is inherited in an autosomal recessive pattern. It may also be caused by trauma, dietary problems and neoplasia. In this condition, the mandible is abnormally long in relation to the maxilla, which results in failure of the incisors to wear normally and causes impaired mastication. The congenital form appears at 8-10 weeks of age. Clinical signs related to malocclusion include anorexia, dysphagia, bruxism, ptyalism, weight loss, and dental disease. Depending on the primary cause, treatment is corrective burring or extraction of affected teeth with supportive care and a change to a higher fiber diet.

2. Congenital Glaucoma
   Congenital glaucoma or buphthalmia is an autosomal recessive condition of New Zealand white rabbits. One or both eyes may be affected. The globe is enlarged due to increased intraocular pressure as a result of the absence or underdevelopment of the aqueous humor outflow channels with incomplete cleavage of the iridocorneal angles by three months of age. Corneal edema, scarring and/or cataracts may also be present in the affected eye(s). Histologically, there may be abnormal insertion of the uveal tissue onto the cornea and a lack of pectinate fibers with poor definition of the ciliary cleft and trabecular meshwork.

3. Splayleg
   Splayleg is a descriptive term applied to a condition in which rabbits lack the ability to adduct one or all legs and come to a standing position. This condition may be due to inherited syringomelia, hypoplasia pelvis, femoral luxation and distal foreleg curvature.

4. Endometrial Venous Aneurysms
   Endometrial venous aneurysms are considered congenital defects characterized by multiple blood filled endometrial varices that are composed of dilated, thin walled veins that rupture and bleed periodically into the uterine lumen.
CONGENITAL DISEASES REFERENCES:


MISCELLANEOUS CONDITIONS

1. **Vertebral fracture**
   The skeleton composes only 6-8% of the total body weight of the New Zealand white rabbit versus 12-13% of a cat’s body weight. The bones of a rabbit are relatively fragile and fractures occur readily, especially with improper handling. Vertebral fractures are caused by improper handling leading to sudden, unsupported movement of the hindlimbs that causes fracture and less commonly vertebral luxation. Most fractures occur in the lumbosacral region, cause spinal cord damage, and produce paralysis and urinary incontinence.

2. **Trichobezar**
   Trichobezar or “wool block” are masses of hair and ingesta in the stomach that result from excessive self-grooming. They are common and are usually an incidental finding. Predisposing factors may include low fiber diets, experimental manipulation and stress. Trichobezars may cause complete or partial obstruction with subsequent gastric rupture and peritonitis. Anorexia and fatty liver can also be seen. Gastrotomy to remove the blockage may be required as a life-saving measure.

3. **Barbering**
   Barbering or hair chewing is most common in young and group housed rabbits. It is characterized by alopecia without dermatitis on the face and back. Boredom and low roughage diets are considered to be predisposing factors. The differential diagnosis for hair loss includes hair pulling for nests, behavioral problems, malnutrition, ectoparasites, dermatophytosis, bacterial infections, cage rubbing and seasonal molting.

4. **Cataracts**
   Spontaneous cataracts have been observed in New Zealand white rabbits during toxicologic studies as an incidental finding. An autosomal recessive mode of inheritance is suggested.

5. **Urine scalding**
   Urine scalding can occur as a result of the following problems: primary incontinence due to neurological conditions, conditions that prevent the rabbit from adopting a correct stance for urination, conditions that prevent normal grooming, calcium carbonate deposits in the bladder sediment, anatomical defects, poor husbandry and reproductive disease resulting in perineal inflammation. Secondary bacterial infection is common. Treatment is clipping and cleaning the affected area and antibiotics if needed.

6. **Myocardial degeneration and necrosis**
Certain drugs including catecholamines and the anthracycline antibiotics have been reported to cause myocardial degeneration and necrosis in rabbits. There is a report of suspected myocardial damage due to the administration of ketamine/xylazine anesthesia. The authors believe it may be due to impairment of coronary blood flow due to coronary artery constriction with ischemia.

7. Prolapse of the Deep Gland of the Third Eyelid

Prolapse of the deep gland of the third eyelid has been recently reported and appears clinically as a protrusion of a large tissue mass from the medial canthus of the eye. Histologically, the mass is composed of bilobated glands arranged in an alveolar-like pattern without inflammation. The cause is proposed to be abnormal laxity of the supporting connective tissue.

8. Spontaneous Ocular Lesions

The most commonly affected ocular segments are the cornea and lens; the cornea tends to be more affected in males, presumably due to more fighting and playing. Cataracts were the most common lesion affecting the lens.

MISCELLANEOUS CONDITIONS REFERENCES:


NEOPLASTIC/PROLIFERATIVE DISEASES

1. Reproductive System:

   Uterine adenocarcinoma is the most common spontaneous neoplasm of the rabbit. The incidence increases with age and nearly all breeds are affected. The role of estrogens is equivocal. Grossly, there are multiple, nodular thickenings that protrude into the uterine lumen. Histologically, these thickenings are composed of acinar and tubular structures supported by a vascular myxoid stroma. There is serosal implantation and metastasis to the lung, liver, and regional lymph nodes. A uterine choriocarcinoma with metastasis to the lung and mesentery has been recently reported.

   Leiomyoma/leiomyosarcoma has been reported as incidental findings at necropsy.

   Mammary carcinoma has been reported frequently in laboratory rabbits. Cystic hyperplasia progresses to benign neoplasia with progresses to invasive adenocarcinoma. Metastasis is to the lungs and regional lymph nodes.

   In the testis, interstitial cell tumor is the most common neoplasm. There is a single report of gynecomastia associated with a testicular interstitial cell tumor in a
buck. Sertoli cell tumors and seminomas have also been reported. A testicular granular cell tumor in a pet rabbit has been reported.

2. Nervous System
   Pituitary adenoma occurs in aged New Zealand white rabbits. Some secrete prolactin that can cause mammary gland hyperplasia and dysplasia. Rabbit mammary tissue is especially responsive to prolactin. Blood prolactin levels can be measured and pituitary glands can be imaged by computed tomography. There is a recent case report of a prolactin-secreting pituitary adenoma with development of a cystic mammary adenocarcinoma in a New Zealand white rabbit.

   Neurofibromas, neurofibrosarcomas and malignant peripheral nerve sheath tumors have been reported. As in other species, they are locally invasive and very difficult to completely surgically excise. Recurrence is common.

3. Musculoskeletal System:
   Osteosarcoma is rarely reported in the rabbit. It can occur in the mandible, ribs, long bones and extraskeletal locations. As in other animals, metastasis is common and is usually to the lungs and lymph nodes. There is a single report of an extraskeletal fibroblastic osteosarcoma in a rabbit that occurred in the lip.

   An ossifying fibroma was reported in the right maxillary region of a miniature rex rabbit.

4. Respiratory System:
   Mesothelioma has been reported in the rabbit.

5. Gastrointestinal System:
   Bile duct adenoma and bile duct adenocarcinoma have both been reported as incidental findings at necropsy. These neoplasms have minimal clinical significance.

   A solitary biliary hamartoma with cholelithiasis was reported from a single transgenic New Zealand white rabbit.

6. Urinary System:
   Renal cell carcinoma and nephroblastoma have been reported in the rabbits. Nephroblastoma or embryonal nephroma may be single or multiple and affect one or both kidneys. They are slow growing and are unlikely to metastasize.

7. Hematolymphatic System:
   Lymphoma is most common in juvenile and young adult rabbits. It is typically the visceral form that involves the liver, spleen, and kidney, although rare localized forms have been reported. Occasionally, leukemia is present. At necropsy, there is lymphadenopathy, splenomegaly, and hepatomegaly with multiple, white circumscribed nodules. Histologically, the neoplastic cells are lymphoblastic. Both B-cell and T-cell types have been observed. There is a single report of a B-cell lymphoma in the Harder’s gland of the rabbit.

   Thymoma occurs in rabbits at a low incidence and is usually diagnosed at necropsy as an incidental finding, however, radiographic examination often reveals an anterior mediastinal mass with enlarged cardiac silhouette with pleural effusion. It may cause coughing, tachypnea, dyspnea and exercise intolerance. Thymomas have been associated with paraneoplastic syndromes such as myasthenia gravis, autoimmune disease, and hypercalcemia of malignancy, etc. Recently, exfoliative dermatitis was
reported in a case of thymoma in a rabbit. There were many similarities seen with exfoliative dermatitis in cats secondary to thymoma.

8. Integumentary System/Mesenchymal:

Trichoblastoma, a benign cutaneous neoplasm of hair follicle origin is not uncommon. Viral-induced tumors include shope fibroma and papilloma were discussed under the virus section. Squamous cell carcinomas, other hair follicle tumors, and sebaceous gland carcinoma have also been reported. Lipoma, liposarcoma, myxosarcoma, fibrosarcoma, hemangiosarcoma and malignant melanoma have all been reported.

NEOPLASTIC DISEASE REFERENCES:

GENERAL RABBIT REFERENCES: