

# INFECTIOUS AGENT EXCLUSION LIST FOR RATS

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Specific examples of interference to research caused by infectious agent exposure are viewable at <http://www.lal.org.uk/pdffiles/GVSOLAS.pdf>.

## I. DNA VIRAL DISEASES

### PARVOVIRUS

**Etiology:** 3 major antigenic groups represented by Kilham's rat virus (KRV or RV), Toolan's H-1, rat parvovirus (RPV, formerly ROPV, rat orphan parvovirus); conserved nonstructural proteins so IFA for serodetection; small, single strand DNA, nonenveloped.

**Transmission:** oronasal, fomites, transplacental, transmammary; shedding in urine, feces, milk, oropharynx; common; relatively resistant, remain infectious at room temperature.

**Clinical:** KRV/RV most pathogenic, perhaps only strain that causes disease following natural exposure (H-1 and RPV are nonpathogenic); experimental neonatal exposure predilection for primordial cells of cerebellar cortex, periventricular region, hepatocytes, endothelial cells, bone marrow; no intestinal mucosal lesions as in other species; brain, liver, and testes affected.

**Pathology:** multiple foci of hemorrhage in cerebrum and cerebellum with malacia, testes and epididymis with coagulative necrosis, liver with focal necrosis; damaged endothelial cells and megakaryocytes; neonates with cerebellar hypoplasia, hepatitis, jaundice; abortion, fetal resorption, infertility; scrotal hemorrhage, peritesticular fibrinous exudation.

**Significance:** inapparent enzootic common; contaminate transplantable tumors, cell lines, viral stocks.

## II. RNA VIRAL DISEASES

### A. CORONAVIRUS

#### RCV/SDAV

**Etiology:** Rat Coronavirus, numerous strains, varied virulence; sialodacryoadenitis virus (SDAV), Parker's rat coronavirus (PRC) initial isolate.

**Transmission:** nasal secretions and saliva.

**Clinical:** subclinical to high morbidity, no mortality; sniffing, blepharospasm, epiphora, intermandibular swelling, chromodacryorrhea porphyrin-containing encrustation around eye; megaloglobus, hyphema, corneal ulcers.

**Pathology:** sialodacryoadenitis of parotid and submandibular salivary, and infraorbital, exorbital, and Harderian lacrimal glands with coagulation necrosis of ductal and acinar epithelial cells with effacement of normal architecture and squamous metaplasia, mononuclear cell infiltration; hyperplastic cervical lymph nodes; regeneration of acinar and ductal structures within 4 weeks; necrotizing rhinitis, tracheitis, bronchitis, alveolitis possible, but transient.

**Ddx:** nasal/ocular discharge associated with mycoplasma, Sendai, PVM; subcutaneous edema of head with *Pseudomonas aeruginosa*; chromodacryorrhea is not diagnostic (porphyrin from Harderian glands) but also caused by high environmental ammonia, stress.

**Significance:** periodic outbreaks with high morbidity; permanent ocular damage; co-pathogen with *Mycoplasma pulmonis*, CAR bacillus; EGF depletion.

### B. PARAMYXOVIRUS

#### PVM

**Etiology:** *Pneumovirus*, pneumonia virus of mice (PVM).

**Transmission:** common enzootic infections; affinity for respiratory epithelium and endothelium; wide host range including mice, hamsters, guinea pigs, gerbils.

**Clinical:** nasal, ocular discharge.

**Pathology:** multifocal, nonsuppurative vasculitis and interstitial pneumonitis with necrosis; prominent perivascular mononuclear cell infiltrates, and BALT hyperplasia.

**Ddx:** Sendai, SDAV.

**Significance:** respiratory pathogen; copathogen with *Mycoplasma pulmonis*; interspecies transmission possible; more commonly a cause of morbidity in immunocompetent rats than mice, perhaps in part due to high degree of BALT hyperplasia.

### SENDAI VIRUS

**Etiology:** *Parainfluenza 1*, (Sendai, Japan).

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**Transmission:** highly contagious, direct contact, aerosol; wide host range including mice, hamster, guinea pig; descending respiratory infection.

**Clinical:** typically subclinical or mild in rats; widespread seroconversion; nasal discharge.

**Pathology:** rhinitis; multifocal, hyperplastic, suppurative, necrotizing bronchitis, bronchiolitis and alveolitis; prominent perivascular and peribronchial mononuclear cell cuffing.

**Ddx:** PVM, coronavirus (SDAV), *Mycoplasma pulmonis*.

**Significance:** primary respiratory pathogen, copathogen; interspecies transmission.

### C. OTHER VIRUSES

**Adenovirus** – seroconvert to MAD-2 (K87), no morbidity, incidental intranuclear inclusions in small intestinal enterocytes.

**Hantavirus** – zoonotic hazard; aerosol, contact with infected urine; no clinical disease in rats; also naturally infects *Peromyscus* mice; 2 major lineages, (HFRS) Hemorrhagic Fever and Renal Syndrome in humans with fever, thrombocytopenia, myalgia, headache, petechiae, retroperitoneal and renal hemorrhage; (HPS) Hantavirus Pulmonary Syndrome in humans with fever, pulmonary edema, shock; Bunyviridae.

**Herpesvirus** – Rat Cytomegalovirus (RCMV) rare to nonexistent in laboratory colonies; cytomegaly, intracytoplasmic and intranuclear inclusions in salivary and lacrimal gland ductal epithelium.

**Papovavirus** – Rat Polyoma virus, single report, nude colony, pneumonia and parotid sialoadenitis.

**Poxvirus** – Eastern Europe, Turkmenia rodent poxvirus, related to cowpox, clinically resembles mousepox.

**Rat Cardiovirus** – (RCaV), asymptomatic; also seroconversion to TMEV-GDVII and MEV.

**Rotavirus** – Infectious Diarrhea of Infant Rats (IDIR), multinucleate syncytia, pathogenesis similar to EDIM in mice, possible human source.

**Rat Leukemia Virus** – endogenous proviral sequences in 100% rats.

## III. BACTERIAL DISEASES

### A. GRAM NEGATIVE ENTERIC

#### TYZZER'S DISEASE

**Etiology:** *Clostridium piliforme*, filamentous, spore-forming, obligate intracellular.

**Transmission:** ingestion; weanlings; spore contaminated bedding infectious >1 year; wide host range, but isolates tend to be host specific.

**Clinical:** low morbidity, variable mortality; typical triad of enterohepatic disease with secondary myocardium; dilation of ileum, miliary hepatic foci.

**Pathology:** segmental transmural necrotizing ileitis (megaloileitis); multifocal hepatitis to coagulation necrosis; focal myocardial necrosis; Giemsa, Warthin-Starry, PAS-positive intracytoplasmic bundles of filamentous bacilli.

**Ddx:** salmonellosis, chloral hydrate IP.

**Significance:** spore persistence; morbidity; interspecies transmission, potential zoonosis to immunocompromised humans.

#### SALMONELLOSIS

**Etiology:** *Salmonella enteritidis* serotypes *enteritidis* and *typhimurium*

**Transmission:** orofecal; contaminated feed, bedding.

**Clinical:** subclinical; diarrhea, chromodacryorrhea.

**Pathology:** ileum and cecum fluid distended, flecks of blood, thickened wall; ulcerative enteritis typhilitis with ileal crypt hyperplasia and leukocytic infiltration of lamina propria; hyperplastic Peyer's patches, mesenteric lymph nodes, spleen; focal necrosis and hemorrhage of splenic red pulp; focal hepatic coagulation necrosis.

**Ddx:** Tyzzer's, pseudomoniasis, rotavirus, cryptosporidiosis; detected using selenite-F plus cystine broth overnight followed by streaking on brilliant green agar.

**Significance:** interspecies transmission; potential zoonotic.

*Helicobacter colis* – individual report of ulcerative typhlitis in nudes; also *H. trogontum* as potential gastrointestinal pathogen.

*Lawsonia intracellularis* – emerging enteric pathogen; wide host range.

## B. GRAM NEGATIVE RESPIRATORY

### BORDETELLA

**Etiology:** *Bordetella bronchiseptica*.

**Transmission:** aerosol; colonizes apices of respiratory epithelium; uncommon opportunistic pathogen; common upper respiratory inhabitant of guinea pig (and important primary pathogen) and rabbit (potential copathogen).

**Clinical:** nasal discharge.

**Pathology:** suppurative rhinitis, anteroventral suppurative bronchopneumonia with consolidation.

**Dx:** readily culturable small blue-gray colonies of motile bacillus.

**Significance:** uncommon, opportunistic, secondary co-pathogen with concurrent infections of *Mycoplasma pulmonis*, PVM, Sendai, or coronavirus.

### CAR BACILLUS

**Etiology:** Cilia-Associated Respiratory (CAR) Bacillus; filamentous, argyrophilic bacillus with gliding motility; difficult to culture; survives freezing & thawing.

**Transmission:** contact, infected dams, contaminated bedding; colonizes respiratory ciliated epithelium; wide host range including mice, rabbits, cattle, pigs.

**Pathology:** chronic suppurative bronchitis and bronchiolitis with marked peribronchiolar leukocytic infiltration; mucopurulent bronchopneumonia progressing to bronchiectasis; Warthin-Starry staining shows numerous slender bacilli inserted along apices of ciliated respiratory epithelium.

**Ddx:** experimental intranasal inoculation results in lesions similar to *Mycoplasma pulmonis*, but natural respiratory disease usually mixed infection.

**Significance:** primary or secondary pathogen; importance and prevalence developing and require further study.

### MYCOPLASMOSIS

**Etiology:** *Mycoplasma pulmonis*, only clinically significant *Mycoplasma*, lacks cell wall, fastidious, requires selective media; chronic respiratory disease (CRD), murine respiratory mycoplasmosis (MRM); *M. neurolyticum* mice only.

**Transmission:** aerosols, months to establish infection, disease 6 months post-infection, intrauterine possible; CRD multifactorial including *Mycoplasma*, Sendai, CAR bacillus, coronavirus, ammonia >25 ppm.

**Clinical:** nasal discharge, respiratory distress, sniffing, chromodacryorrhea, torticollis, infertility; affinity for epithelial cells of respiratory tract, middle ear, endometrium.

**Pathology:** anteroventral plum-colored pulmonary abscessation, purulent nasal turbinates, tympanic bullae, uterine horns, ovarian bursae; hyperplasia and cuboidal to squamous metaplasia of respiratory epithelium, characteristic lymphoplasmacytic peribronchiolar cuffing, progression to bronchiectasis and bronchiolectasis; perioophoritis, endometritis.

**Ddx:** false seronegative up to 4 months after exposure; false seropositives possible since *M. arthritidis* cross-reacts serologically; concurrent Sendai, CAR bacillus, coronavirus, additive effect; concurrent opportunistic bacteria *Pasteurella*, *Bordetella*, diplococci; cultivation with SP-4 formula.

**Significance:** major pathogen in rats, persists, antibiotics no merit; respiratory, infertility, immunomodulation.

### PASTEURELLA

**Etiology:** *Pasteurella pneumotropica*, coccobacillus.

**Transmission:** orofecal, direct contact; commonly colonizes the intestine.

**Clinical:** inapparent commensal infection of nasopharynx, conjunctiva, uterus, lower respiratory.

**Pathology:** frequently isolated in the absence of disease; potential opportunistic pathogen associated with primary pathogens *Mycoplasma pulmonis* or Sendai; interstitial pneumonitis, rhinitis, otitis media, mastitis, pyometra, fetal death, resorption.

**Ddx:** other pyogenic bacteria, *Staphylococcus*, *Corynebacterium*, *Pseudomonas*.

**Significance:** opportunistic secondary infection.

*Haemophilus sp.* – lower respiratory isolate, single report.

## C. GRAM POSITIVE

## CORYNEBACTERIUM

**Etiology:** *Corynebacterium kutscheri*, gram-positive, diphtheroid bacillus with “Chinese letter” configurations *in situ*.

**Transmission:** inapparent infection oropharynx, cervical lymph nodes; mice, rats, and guinea pigs;

**Clinical:** exacerbated by immunosuppression or concomitant disease; hematogenous spread to lungs, kidneys, liver; chromodacryorrhea, mucopurulent nasal discharge, respiratory distress.

**Pathology:** raised, pale, coalescing foci of pulmonary suppuration; also kidney and liver; multifocal coagulation to caseous necrosis with neutrophilic infiltration not associated with airways; “Chinese letter” amorphous basophilic bacterial colonies; lymphoid hyperplasia.

**Dx:** carriers detected by oropharyngeal washes or cervical lymph node cultures.

**Significance:** inapparent carriers.

## STAPHYLOCOCCUS

**Etiology:** *Staphylococcus aureus*, coagulase positive.

**Transmission:** present on skin of clinically normal carriers.

**Clinical:** ulcerative dermatitis, self-trauma, males, frequently shoulder, head, neck and ears.

**Pathology:** sharply demarcated ulcerative dermatitis with epidermal coagulation necrosis and discrete colonies of coccoid bacteria in overlying necrotic debris.

**Ddx:** bite wounds, mycotic infection, rarely epitheliotropic lymphoid tumors (mycosis fungoides).

**Significance:** sporadic, males.

## STREPTOCOCCUS

**Etiology:** *Streptococcus pneumoniae*, diplococcus.

**Transmission:** carried in the nasoturbinates & tympanic bullae of clinically normal rats; polysaccharide capsule resists phagocytosis; activates alternate complement cascade.

**Clinical:** asymptomatic; adolescents, serosanguinous to mucopurulent nasal discharge, rhinitis, conjunctivitis, vestibular signs; acute primary disease or secondary infections.

**Pathology:** fibrinopurulent polyserositis, pleuritis, peritonitis, pericarditis, periorchitis, meningitis; suppurative otitis media and rhinitis; fibrinopurulent bronchopneumonia; embolism.

**Ddx:** *Corynebacterium*, *Salmonella*, *Pseudomonas*, *Pasteurella*; impression smears with encapsulated diplococci; alpha hemolysis on 5% blood agar.

**Significance:** acute systemic disease; mortality; potential zoonosis; mice can become infected, but unlike rats rarely develop disease.

## D. OTHER BACTERIAL INFECTIONS

### PSEUDOMONAS

**Etiology:** *Pseudomonas aeruginosa*, gram-negative bacillus.

**Transmission:** sipper tubes; water; fomites, ungloved hands; grows at room temperature; asymptomatic carriers 5-20%; predisposing factors that produce neutropenia.

**Clinical:** dyspnea, high mortality.

**Pathology:** acute coagulation necrosis with suppuration, and obliteration of pulmonary architecture; abscessation of lung, spleen, kidney; thromboembolism, vegetative endocarditis (catheter sequellae); visceral ecchymoses.

**Ddx:** *Corynebacterium*, *Pasteurella*, *Salmonella*, *Mycoplasma*; identifiable with Brown and Brenn tissue gram stain; Kosher's citrate medium.

**Significance:** important cause of disease, mortality.

***Enterococcus faecium-durans-2*** – single report; sucklings, enteritis, diarrhea; high morbidity & mortality.

***Erysipelas rhusiopathiae*** – single report; fibrinopurulent polyarthritis, endocarditis, myocarditis.

***Hemobartonella muris*** – historical, uncommon; transmitted by *Polyplax spinulosa*; extra-erythrocytic parasite; inapparent, splenomegaly, reticulocytosis.

***Klebsiella pneumonia*** – fecal isolate, normal animals; rare, opportunistic mild upper respiratory pathogen, abscessation.

***Leptospira icterohemorrhagiae*** – subclinical; urinary transmission; possible zoonosis.

***Streptobacillus moniliformis*** – gram-negative peomorphic filamentous rod; commensal, nasopharynx; opportunistic respiratory pathogen in concert with CAR bacillus or *Mycoplasma*; wound abscessation; potential zoonosis – rat bite fever, Haverill fever; *Spirillum minus* also a cause of rat bite fever in feral rats.

Idiopathic – Eosinophilic Granulomatous Pneumonia in Brown Norway Rats – eosinophilic-rich granulomatous pneumonitis; perhaps, inadvertent allergen exposure; Brown Norway model of asthma pathogenesis – readily develop increased bronchiolar responsiveness and elevated IgE postexposure to allergens.

#### IV. MYCOTIC INFECTIONS

##### DERMATOPHYTOSIS

**Etiology:** *Trichophyton mentagrophytes*.

**Transmission:** asymptomatic carriers, fomites; relatively rare florid skin infections;

**Clinical:** neck, back, base of tail, patchy hair loss, raised erythematous, pustular dermatitis.

**Pathology:** hyperkeratotic, hyperplastic dermatitis with folliculitis; arthrospores in hair shaft, PAS or methenamine silver stains.

**Dx:** skin scrapings in 10% KOH.

**Significance:** interspecies spread, wild rodents, human contacts.

##### PNEUMOCYSTIS

**Etiology:** *Pneumocystis carinii*, attached to type I pneumocytes by filopodia.

**Transmission:** asymptomatic carriers; numerous hosts harbor, mice, rabbit, cat, horse, dog, monkey; but species-specific strains.

**Clinical:** dyspnea, cyanosis.

**Pathology:** consolidation; opaque, pale pink lungs do not collapse; alveolar flooding with foamy eosinophilic exudates with coccoid yeast-like cysts and trophozoites; honeycomb appearance; severe interstitial pneumonitis; marked proliferation of type II pneumocytes and interstitial fibrosis.

**Dx:** organisms in histosections visualized with Grocott modification of Gomori's methenamine silver stain; impression smears of lung stained with Giemsa.

**Significance:** athymic; immunosuppressed; no interspecies transmission.

***Aspergillus fumigatus*** or *A. niger* – chronic rhinitis, hyperplasia, squamous metaplasia; fungal hyphae with PAS or silver stains.

#### V. PARASITIC INFESTATIONS

##### A. ECTOPARASITIC INFESTATIONS

(not an important consideration)

***Polplax spinulosa*** – pruritis, anemia; lice vector of *Hemobartonella muris*.

***Xenopsylla*, *Leptopsylla*, *Nosopsyllus*** – rare fleas.

***Radfordia ensifera (Myobia ratti)*** – fur mite, pruritis, alopecia, only common ectoparasite in laboratory rats, except typically non-pathogenic.

***Ornithonyssus bacoti*** – nonselective tropical rat mite; pruritic; refuge in surrounding environment.

***Notoedres muris*** – burrows in cornified epithelium of ear.

##### B. ENDOPARASITIC INFESTATIONS

##### PROTOZOANS

***Giardia muris*** – flagellate, small intestine surface mucosa, typically nonpathogenic; immunosuppression resulting in low grade catarrhal enteritis.

***Spironucleus muris*** – flagellate, crypts, typically nonpathogenic, catarrhal enteritis.

***Cryptosporidium parvum*** – asymptomatic, single report, transient, mild, diarrhea.

***Eimeria sp.*** – rare in rats, proliferative, coccidial enteritis.

## NEMATODES

***Syphacia obvelata*, *Syphacia muris*** – Oxyuriasis – pinworms; common, eggs resistant & drift; direct life cycle of 12-15 days, emerge in cecum, thread-like, females migrate to deposit eggs on perineum; tape test, banana-shaped asymmetrical ova; subclinical, young particularly susceptible, rectal prolapse possible; colitis.

***Aspicularis tetraptera* – Oxyuriasis** – pinworms; common, eggs resistant & drift; direct life cycle of 23-25 days; emerge in cecum, thread-like, lay eggs in terminal colon; flotation, bilaterally symmetrical ova; subclinical, young particularly susceptible, rectal prolapse possible; colitis.

***Trichosomoides crassicauda*** – bladder thread worm; asymptomatic, urinary tract, intracage transmission, present in renal pelvis and urinary bladder.

## CESTODES

***Hymenolepis nana*** – “dwarf tapeworm”, direct (20-30 days) or indirect arthropod intermediate cycles possible; small flattened (1mm wide) serrated adults in small intestine the size of villi; wide host range; interspecies spread, significant hamster endoparasite; potential zoonosis.

***Taenia taeniaformis*** – cat tapeworm; rat is intermediate host of larval form ***Cysticercus fasciolaris*** in liver, sarcomas can develop in reactive zone of fibroplasia surrounding infestation.