BACTERIAL AND FUNGAL INFECTIONS

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BACTERIAL INFECTIONS

NONHEMOTROPIC MYCOPLASMA

- **Nonhemotropic forms:** *M. canis, M. cynos, M. felis, M. gatae, Ureaplasma spp. Etc…*
- Smallest free-living, self-replicating microorganisms
- Gram-negative, lack cell wall (easily damaged)
- Commensal → primary or opportunistic pathogens
  - *M. canis* in dogs and *M. felis* in cats present in laryngeal mucosa + nasopharynx
- Clinical disease usually occurs as a result of immunosuppression or disruption of host barriers

NONHEMOTROPIC MYCOPLASMA: RESPIRATORY IN DOGS

- Normal flora in upper respiratory tract but controversial whether they are present in lower respiratory tract
- Seen in dogs with primary ciliary dyskinesia → prolonged suppurative infection
- Part of Canine Infectious Respiratory Disease (CIRD)
  - *B. bronchiseptica, M. cynos*, viruses (canine influenza virus, canine coronavirus)
- Can evade the immune system → chronic, low grade infection
- *M. cynos* associated with pneumonia in puppies in kennel settings

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SYSTEMATIC REVIEW

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A systematic review and meta-analyses of the association between 4 mycoplasma species and lower respiratory tract disease in dogs

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Background: The pathogenic role of mycoplasmas in the lower respiratory tract (LRT) of dogs is debated, because mycoplasmas can be isolated from both healthy and sick dogs.

Objectives: To critically assess available data from controlled observational studies on the role of 4 mycoplasma species in LRT disease of dogs.

Design: Systematic review and meta-analyses.

Methods: Seven electronic databases were searched for relevant publications. Risk of bias was assessed by the Newcastle-Ottawa Scale. Meta-analyses, stratified by mycoplasmal species, were performed using a random effects Bayesian model with noninformative priors to estimate pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the association between *Mycoplasma cynos*, *Mycoplasma canis*, *Mycoplasma spumans*, and *Mycoplasma edwardii* and LRT disease in dogs.

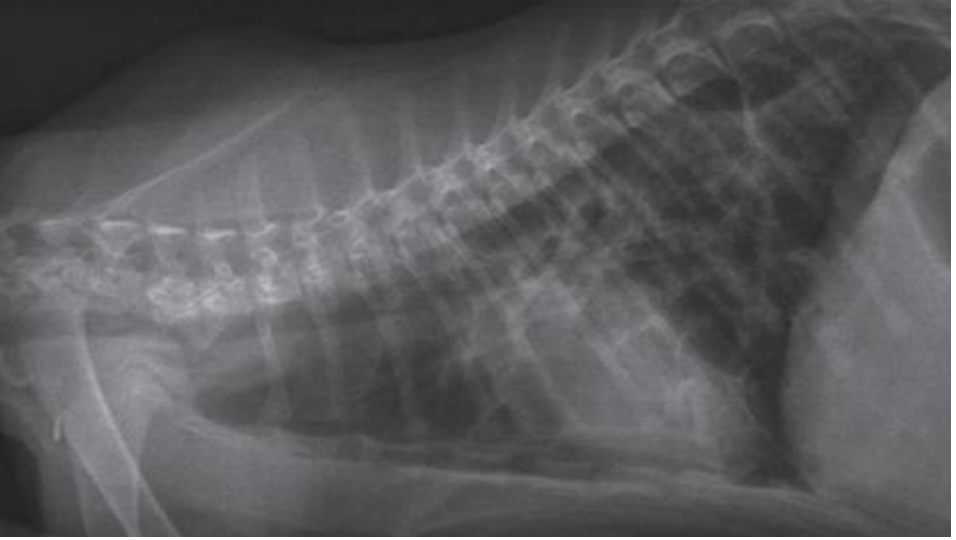
Results: Five studies were included from 1201 references identified. All studies dealt with *M. cynos*, whereas 3 dealt with the other mycoplasma species. A significant association was found between *M. cynos* and LRT disease (Bayesian OR, 3.60; CI, 1.31-10.29). Conversely, *M. canis*, *M. spumans*, and *M. edwardii* were not significantly associated with LRT signs (Bayesian OR, 1.06; CI, 0.10-14.63; Bayesian OR, 3.40; CI, 0.16-54.27; and Bayesian OR, 1.04; CI, 0.05-23.54, respectively).

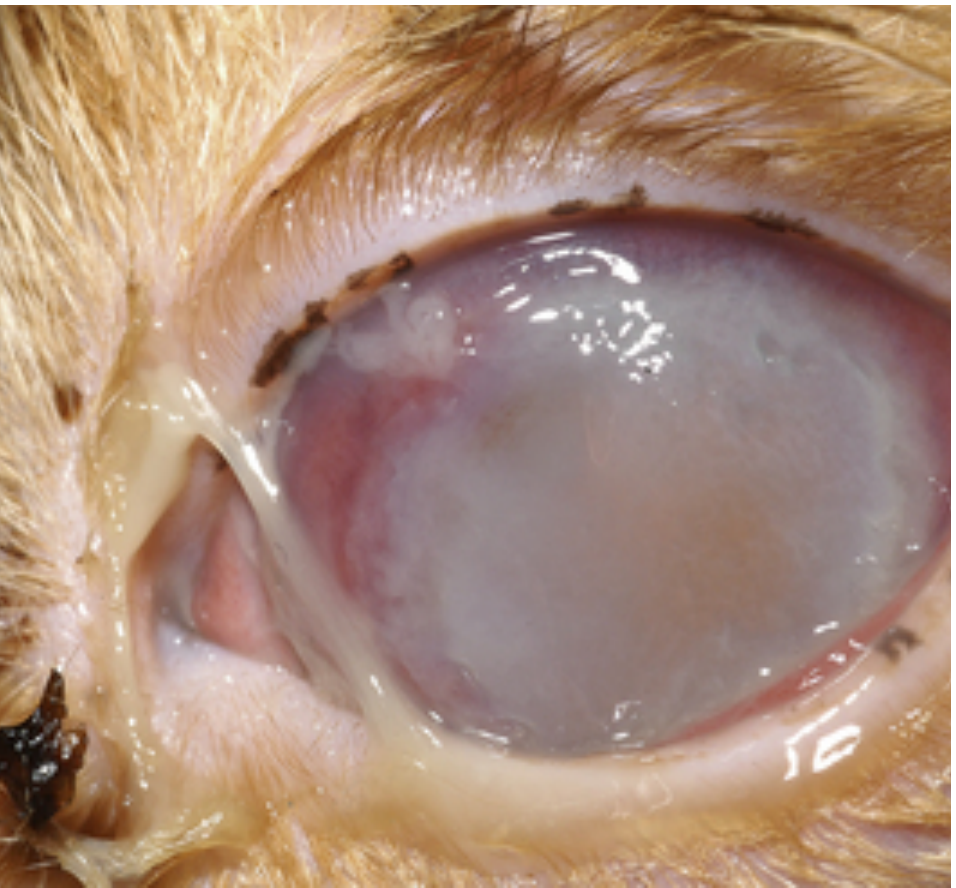
Conclusions and Clinical Importance: Results support a pathogenic role of *M. cynos* and a commensal role of *M. canis* and *M. edwardii* in LRT in dogs. Although the association was not significant based on the CI, the point estimate of the Bayesian OR was relatively high for *M. spumans*, making its role less clear. *Mycoplasma cynos*-specific polymerase chain reaction should be considered on samples from dogs with LRT.

- Mycoplasmas occurred in decreasing frequency from the nasal cavity to the lower airway
- Mycoplasma present in LRT may be due to migration from URT vs oropharyngeal contamination during sampling
- *M canis, M cynos, M edwardii, and M spumans* all have been reported in dogs with LRT disease

RESULTS:

- Significant association between *M cynos* and LRT disease in dogs but not the other
- Unlike previous studies, this study suggested that *M cynos* may have primary pathogenic role
  - However, unsure if the association is casual vs consequential





NONHEMOTROPIC MYCOPLASMA: OCULAR + RESPIRATORY IN CATS

- Contributes to feline upper respiratory diseases but rarely a sole cause
- Co-infection with FHV-1 → keratoconjunctivitis + upper respiratory disease
  - Conjunctival hyperemia progressing to chemosis and induration
  - Stromal ulcerative keratitis and/or keratomalacia
- May affect lower respiratory tract and lead to asthma-like signs
  - Bronchopneumonia (Trow JFMS 2008, Bongrand Can Vet J 2012) and pyothorax (Gulbahar Aust Vet J 2002) also reported in kittens

A systematic review and meta-analysis of the association between *Mycoplasma* spp and upper and lower respiratory tract disease in cats

OBJECTIVE
To critically assess available data from controlled observational studies on the pathogenic role of *Mycoplasma* spp in the upper respiratory tract (URT) and lower respiratory tract (LRT) of cats.

DESIGN
Systematic review and meta-analysis.

SAMPLE
12 studies.

PROCEDURES
Seven electronic databases were searched for relevant publications. Risk of bias was assessed via the Newcastle-Ottawa Scale. Meta-analyses, stratified by URT versus LRT disease, were performed to estimate pooled ORs and 95% confidence intervals (CIs) for the association between *Mycoplasma* isolation and URT or LRT disease. Subanalyses by diagnostic method, sampling site, and environment (shelter vs nonshelter) were planned for studies on URT disease.

RESULTS
A significant association was found between isolation of mycoplasmal organisms and URT disease (pooled OR, 1.65; 95% CI, 1.14 to 2.40) but not LRT disease (pooled OR, 1.56; 95% CI, 0.51 to 4.76). The association with URT disease was only significant when conjunctival or pharyngeal samples from nonshelter cats were analyzed with a *Mycoplasma felis*–specific PCR assay.

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested that *M felis* may be a primary pathogen in cats with URT disease, warranting treatment in infected cats. The environment was important to consider when interpreting a mycoplasma-positive sample because of aclinical carriage, especially in shelter cats. Further investigations are needed to determine the role, if any, of mycoplasmal organisms in LRT disease of cats. (*J Am Vet Med Assoc* 2017;250:397–407)

- Main bacterial respiratory pathogens in cats: *B. bronchiseptica, C. felis, and S. canis*
- Mycoplasma spp is pathogenic in LRT but role in URT is unclear

RESULTS:

- Significant association between *M felis* and URT in non-shelter environment
  - Conjunctival or pharyngeal PCR *M felis* specific PCR assay
  - Suspect high level of aclinical carrier status in shelter cats
- Recommend tx if *M felis* is isolated from a URTI sample of a clinical, nonshelter cat

NONHEMOTROPIC MYCOPLASMA: UROGENITAL

- Normal flora of canine urinary and urogenital mucosa
- Feline urine is impervious to *M. felis and M. gateae*
- Mainly *Ureaplasma* spp. If present in dogs
- Opportunistic infection mostly
- Cx: Pollakiuria, stranguria, hematuria, pyuria, +/- vulvar discharge
  - Only small number needed to induce clinical disease (>1000 CFU/mL is sufficient)

NONHEMOTROPIC MYCOPLASMA

- Other conditions: Polyarthritis (*M. felis, M. gatae, M. spumans, M. edwardii*) and meningoencephalitis (*M. felis, M. canis*)
- Diagnosis:
  - Neutrophilic inflammation +/- presence of mycoplasma found with electron microscopy
  - Histopathology unlikely to be useful as sole diagnostics
  - Cultures = challenging as they are fastidious and difficult to culture
    - Require specialized medium (Hayflick broth, Amies medium, or modified Stuart bacterial-transport medium)
    - Osmotically fragile
    - Slow growing (takes 1-2 weeks)
  - PCR
    - Ocular swabs, oropharyngeal swab, BAL, tracheal wash (dogs), synovial fluid, CSF or pleural fluid

NONHEMOTROPIC MYCOPLASMA

- Tetracycline, macrolides, lincosamides, fluoroquinolones or chloramphenicol
  - Long course due as majority are bacteriostatic → weeks to months of therapy
- Lack of cell wall = resistant to beta-lactams!

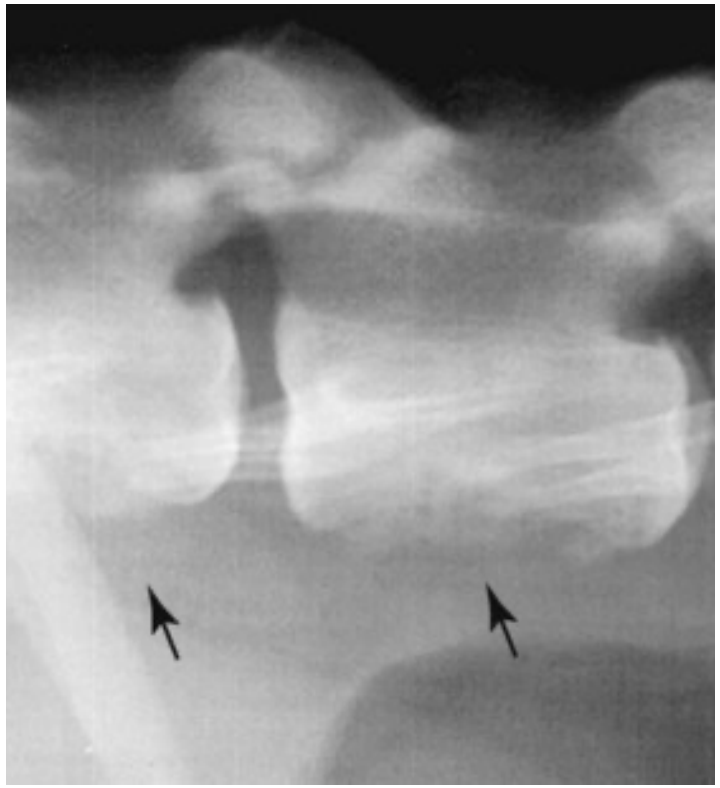
QUESTIONS

- T/F: Mycoplasma has cell wall.
- The most likely pathogenic Mycoplasma species in respiratory tract of dogs is _____ and in cats is _____.
- Which of the following tests is better to isolate Mycoplasma: Culture or PCR?

ACTINOMYCOSIS

- *Actinomyces* spp.
  - G+ve, filamentous
  - Either facultatively anerobic or anaerobic
  - Found in mucous membranes of the oral cavity, GI, and urogenital tracts
  - Opportunistic infection
  - Large breed, outdoor, hunting/working dogs → increased exposure to plant material contaminated with *Actinomyces* spp.

ACTINOMYCOSIS



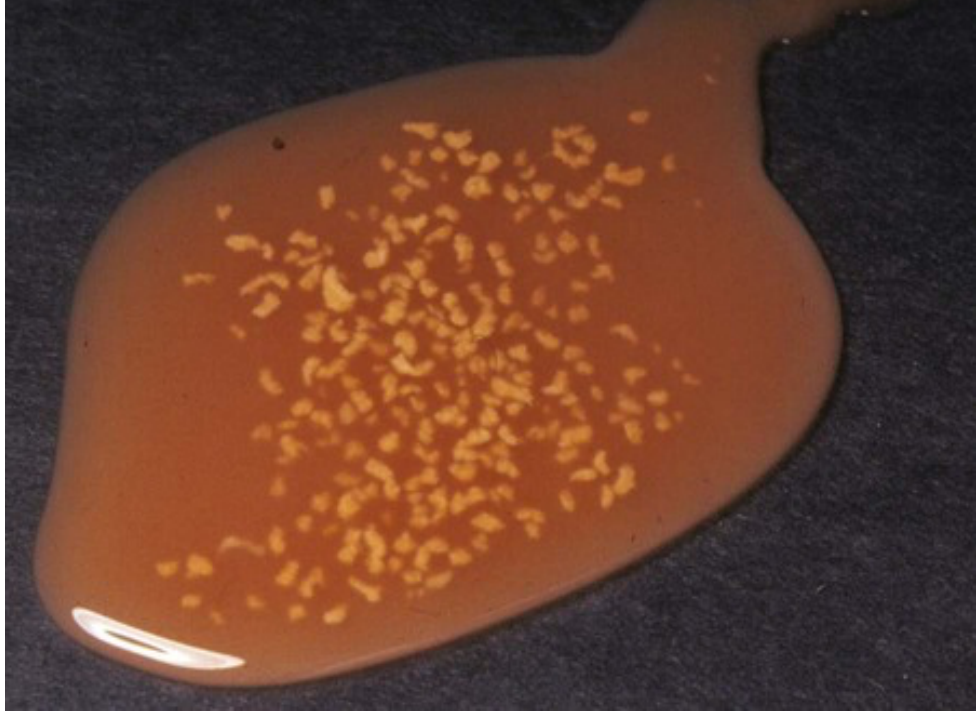
- 3 forms:
  - Cervicofacial
    - From dental dz, oral FB, penetrating wounds to head → acute or chronic infection with swelling, abscesses or mass effects
  - Cutaneous/SQ
    - Single or multiple mass lesions with draining tracts anywhere in the body
  - Thoracic/abdominal forms
    - More common in cats (i.e. pyothorax)
    - Intracavitary effusion with external draining tracts
    - Can be retroperitoneal as well as in CNS (rare)
- Can cause periosteal new bone formation and osteomyelitis if occurring near/on a bony structure

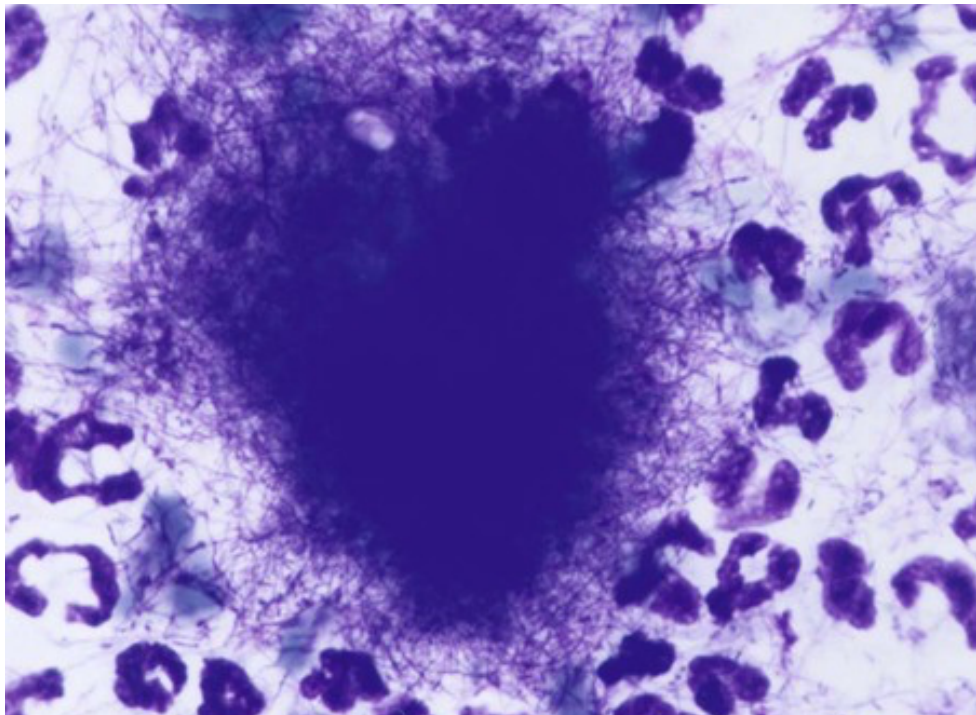
NOCARDIOSIS

- Nocardia spp.
  - Aerobic, g+ve bacteria, branching filamentous bacteria
  - Nonmotile, facultatively intracellular pathogens
  - Ubiquitous environmental saprophytes found in soil, grass, organic material
    - Dry, dusty, windy regions – SW US, Australia
  - Usually in immunocompromised individuals
- Less common than actinomycosis
- Acute to chronic suppurative inflammation
  - Cutaneous/SQ form: Most common in cats, enters host via skin inoculation → local pyoderma
  - Pulmonary form: Pneumonia or pyothorax, dogs > cats
  - Disseminated forms: Rare – suspect systemic spread from pulmonary form

ACTINOMYCOSIS + NOCARDIOSIS

- History: Outdoor exposure
- Cx: anorexia, fever, dyspnea, tachypnea, coughing and depression
- Diagnosis:
  - CBC/Chem: Inflammatory leukogram, anemia, hypoalbuminemia, hyperglobulinemia
  - Nocardia: Ionized hypercalcemia (granulomatous response)
  - Cytology:
    - Suppurative or granulomatous inflammation
    - Dense mats of g+ve filamentous rods +/- branched
  - Nocardia is acid-fast staining
  - Effusion + exudate may contain malodorous, macroscopic sulfur granules
  - Very difficult to grow in culture
  - PCR can be used but MALDI-TOF mass spectrometry is most commonly used





ACTINOMYCOSIS + NOCARDIOSIS

- Drugs INEFFECTIVE for Actinomyces: metro, TMS. Penicillinase-resistant penicillin, cephalexin, aminoglycosides
- Requires prolonged courses of antimicrobials: 6-12 months for Actinomycosis, 3months-1y for Nocardia
- +/- Surgery to address abscess and draining tracts
- Prognosis:
  - Actinomyces: Good for dogs (cure rate >90%), no studies in cats
  - Nocardia: Guarded esp. in disseminated or pulmonary dz

	Actinomycosis	Nocardiosis
Predisposition	Outdoor, male dogs; fight wounds in cats	Immunocompromised patients; fight wounds in cats
Biologic requirements	Facultative or obligate anaerobe	Aerobic
Staining and morphology	Gram positive, rod-shaped, non-acid fast	Gram positive, rod-shaped, partially acid fast
Culture	Challenging to culture; often seen with mixed infections	Typically isolated in pure culture
Preferred empiric antimicrobial	Penicillins	Trimethoprim-sulfamethoxazole
Prognosis	Good, when treated appropriately	Guarded to poor

QUESTIONS

- T/F: Nocardiosis is seen in outdoor male large breed hunting dogs
- T/F: Both diseases have various forms, with subcutaneous/cutaneous presentation being a common finding

CANINE BRUCELLOSIS

- Brucella canis
  - Nonencapsulated, non-spore-forming, facultatively intracellular g-ve coccobacillus
  - Dogs are the only significant hosts
  - Zoonotic but rarely occurs
  - Survive on fomites for days - 8 months depending on environmental conditions
    - Remain viable for months in high humidity, low temp and away from sunlight; can withstand drying
- Venereal transmission most common
  - In utero, via placenta, fetal fluids or vaginal discharge from an infected dam
  - Transmission via blood transfusion and contaminated syringes possible

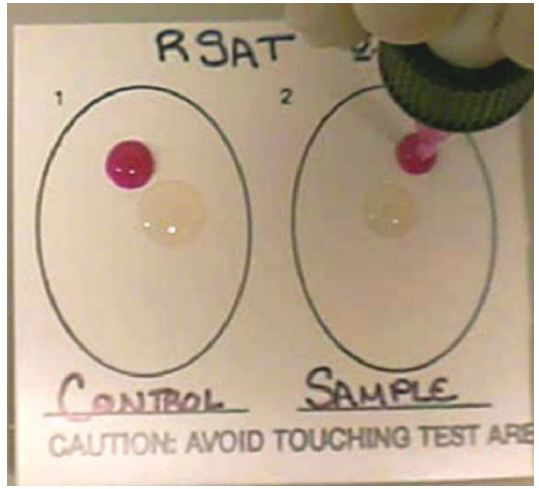
CANINE BRUCELLOSIS

- Attaches to mucous membranes and penetrates epithelial barrier → taken up by mononuclear phagocytic system (intracellular) → travel through reticuloendothelial system to local LN, spleen, liver, +/- BM
- After 7-30 days, it moves into the bloodstream to cause intermittent bacteremia
  - Targets steroid-dependent reproductive tissues: prostate, testes, epididymites, gravid uterus and placenta
- Non-reproductive tissues become infected by bacteremia spreading organisms and antibody-Ag complexes to end-arterial circulation of IVD (Diskospondylitis), eye (uveitis, endophthalmitis)

CANINE BRUCELLOSIS

- Clinical signs
  - Fever is rare
  - Female: Abortion and stillbirths; live pups often die soon after
    - Abortion occurs in last trimester (45-55 days) without premonitory signs → mucoid, serosanguineous or gray-green vaginal discharge persisting for weeks after
    - Early embryonic death + resorption can occur few weeks after mating
  - Male: Epididymitis and scrotal edema (acute) >> orchitis (chronic); scrotal dermatitis (self trauma) → testicular atrophy and infertility (chronic)
  - Lymphadenitis: regional or generalized
  - Diskospondylitis, chronic uveitis, unilateral endophthalmitis, endocarditis, osteomyelitis, meningoencephalitis all reported
- They can spontaneously recover after 1 year from infection, but commonly after 2-3 years
- Death is rare except for in fetus or newborn

CANINE BRUCELLOSIS



- Diagnosis: Use more than 1 test!
  - Cytology to visualize Brucellae from placenta, reproductive discharges with modified Ziehl-Neelsen stain
  - Serology: Can seroconvert as soon as 2-4w after infection
    - Screening test : Rapid slide agglutination test (RSAT), tube agglutination test (TAT), IFA
      - False +ve can occur due to cross-rx with *Bordetella*, *Pseudomonas* etc.
    - Confirmatory test: AGIDcpa (detects LPS, internal cytoplasmic antigen), 2ME-RSAT (detects M-strain B canis)
    - Some tests can cross-react with other g-ve bacteria (E.g. Bordetella, pseudomonas)
  - Culture can be performed on variety of nonselective media or selective media – not always successful
  - Species identification: multiplex PCR, SNP typing, MALDI-TOF MS, MLVA

CANINE BRUCELLOSIS

- Treatment with combination of antibiotics: Tetracycline/FQ with aminoglycosides
  - Doxy 10 mg/kg PO q12h + Gentamicin 5 mg/kg SQ q24h x 7 days then q3w + rifampin 3 mg/kg PO q24h (3 months)
- Quarantine
- No tx is certain to eliminate B. canis and recrudescence possible
  - Can persist in tissue (LN, spleen, uterus, and prostate)
- Disinfection: Killed by most (hypochlorite solution, 70% ethanol, isopropanol, iodophors, phenolic disinfectants, formaldehyde, glutaraldehyde and xylene)
  - Inactivated by acidic pH (<3.5)
  - Destroyed by moist heat (121C/250F) for 15 minutes, dry heat (150-170C/320-338F) for 1 hour, or gamma irradiation

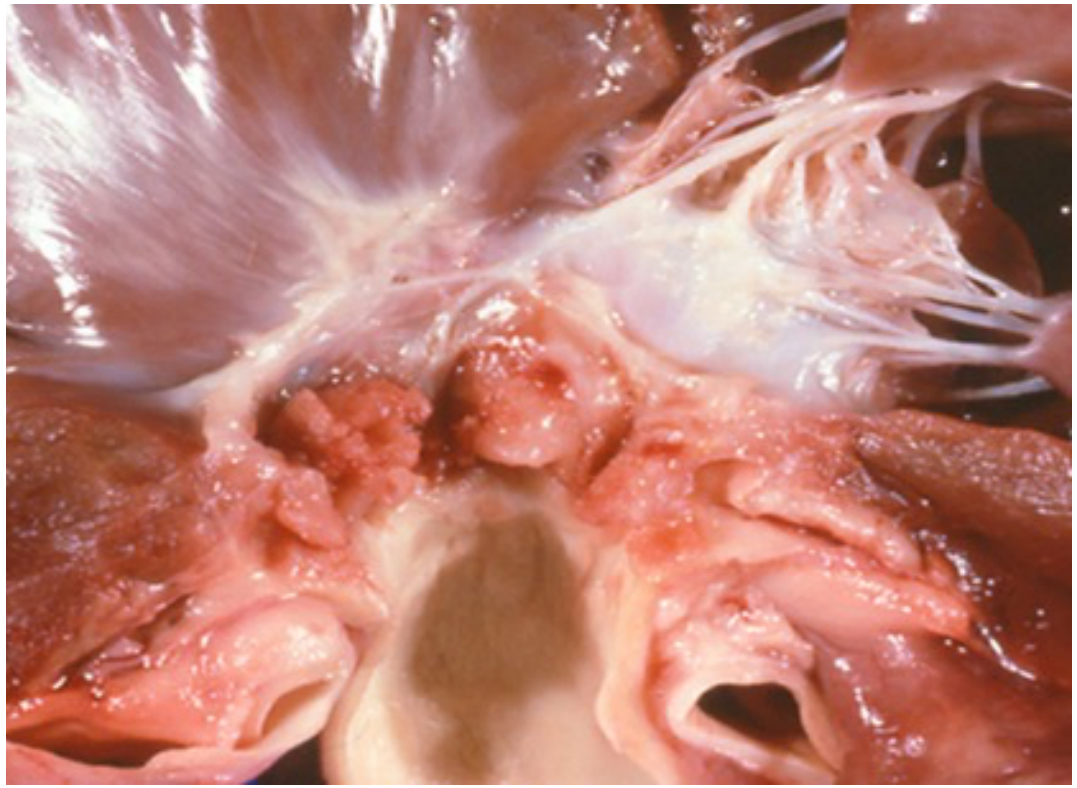
QUESTION

- List 5 body systems that can be affected by Brucellosis?
- What stain should you use to visualize Brucella?
- Treatment options for Brucella?

BARTONELLA

- Thin, short, slightly curved gram –ve hemotropic and rod-shaped bacteria
- Fastidious, slow growing, and facultative intracellular pathogens
- Relevant species: *B. clarridgeiae, B. elizabethae, B. henselae, B. koehlerae, B. quintana, B. rochalimae* and *B. vinsonii berkhoffii.*
  - Cats are reservoir hosts for *B. henselae*
  - Dogs are the main reservoirs for *B. vinsonii berkhoffi*
- Infection begins after inoculation → hematogenous spread leading to Bartonella bacteremia
  - Endothelial cells*, LN, liver, spleen, kidney, dermis and bone marrow are niches where Bartonella are found
- Cx ranges from subclinical bacteremia to vasculitis, meningoencephalitis, lymphadenomegaly, endocarditis/myocarditis, uveitis, skin inflammation etc

BARTONELLA IN DOGS



- More common in tropical environment
- Suspect vector borne but vector not been identified – maybe ticks?
- *Bartonella vinsonii berkhoffi* = most important species
- Infective endocarditis
  - Aortic valve
  - Stimulates endothelial cell function → cell invasion, proinflammatory state, suppression of apoptosis, stimulation of proliferation → vasoproliferative tumor growth (mediated via VEGF)
  - Massive vegetative lesions: Fibrosis, mineralization, endothelial proliferation and neovascularization
- Predisposing factors: living on a farm and roaming, sporting/herding dogs, SAS, bacteremia, immunosuppression (?), recent dental prophylaxis (?)

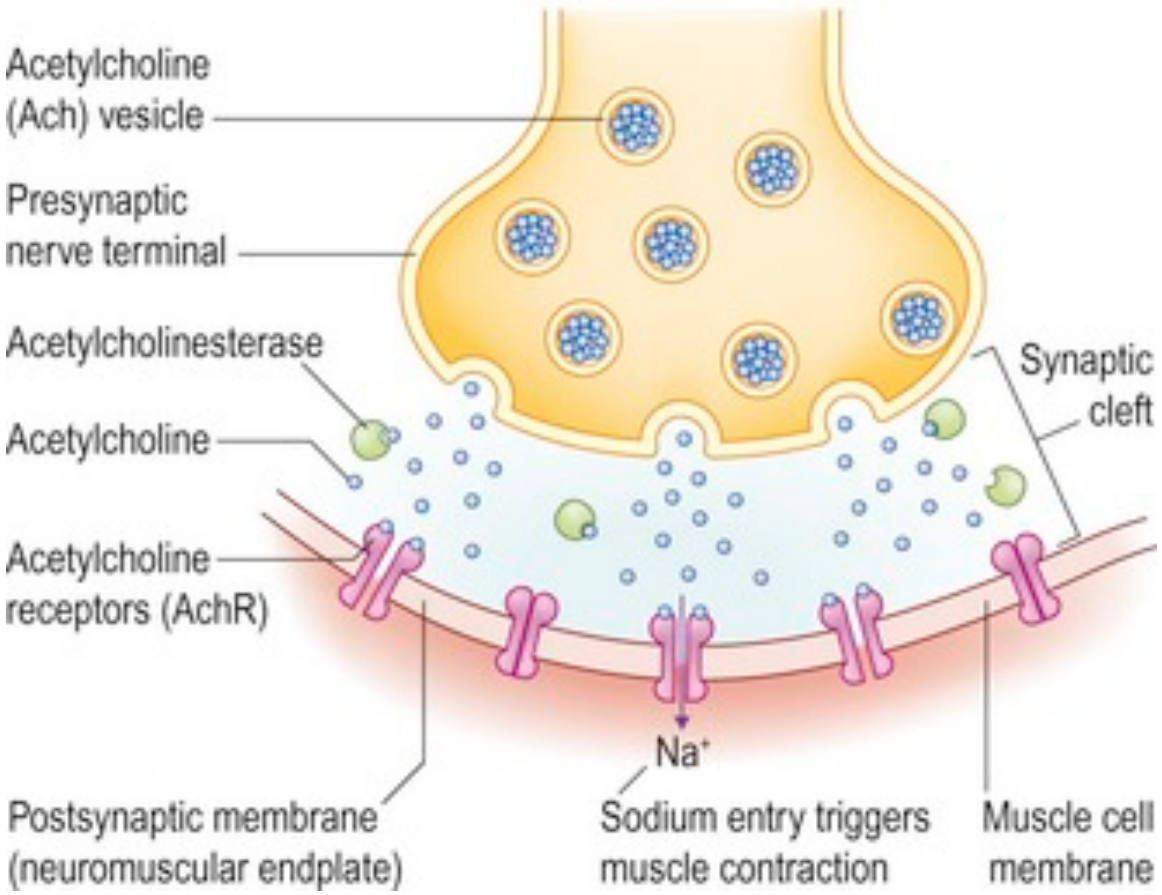
BARTONELLA IN CATS

- *Bartonella henselae (*Cat scratch disease)
- Transmitted to cats via infected fleas or infected blood
- Naturally infected cats are often asymptomatic, subclinical carriers
- FeLV +ve pets may be predisposed
- Cx: Self-limiting, transient, febrile disease lasting 48-72h
  - Rarely causes fever, vomiting, lethargy, red eyes, lymphadenomegaly
  - Recurs during stress (surgery, trauma) or concurrent with other disease

BARTONELLA

- Diagnosis
  - CBC: Neutrophilia leukocytosis thrombocytopenia, anemia (+/- IMHA), eosinophilia
  - Blood or tissue culture = “gold standard’ for confirmation
  - PCR
  - Serology (IFA, ELISA, western immunoblot) can diagnose exposure (4x rise in antibody titer over 2-3 week period)
  - IHC can be used to identify Bartonella antigen in tissue sample
- Treatment: Doxycycline, amoxicillin, enrofloxacin, and rifampin for 4-6 weeks to reduce bacteremia
  - No treatment guideline established to completely clear B. henselae from bloodstream
  - Only tx those with clinical symptoms
- Prevention: Flea preventatives and keep pet indoors

CLOSTRIDIUM



REMINDER OF WHAT NEUROMUSCULAR JUNCTIONS ARE…

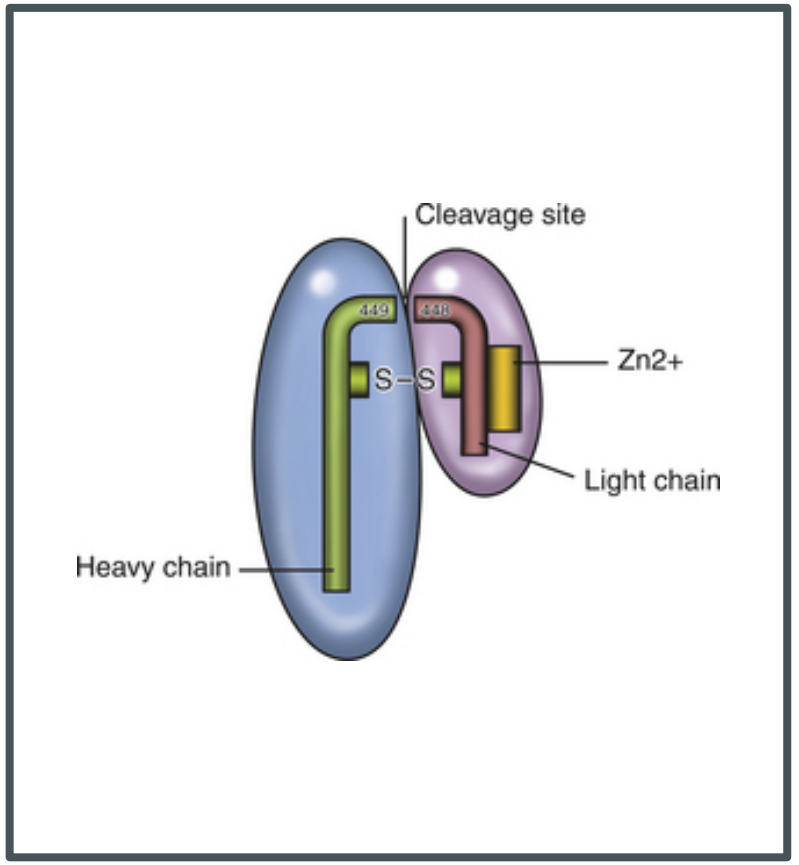
- Acetylcholine (Ach) is carried in synaptic vesicles into the presynaptic nerve terminals
- Action potential arrives at nerve terminal and Ca2+ influx leads to docking of synaptic vesicles to the membrane → Exocytosis of ACh into the synaptic cleft
- ACh binds to AChR on the postsynaptic membrane (motor endplate)
  - Binding triggers Na+ influx → Creates endplate potential, generates and transmit action potential for muscle contraction
- Unbound ACh is metabolized via acetylcholinesterase into choline and acetate

CLOSTRIDIUM

- Botulism and tetanus are caused *C. botulinum* and *C. tetani* respectively
- G+ve, motile, anaerobic spore-forming bacilli
- Spores are infective and they are extremely resistant in the environment (resists alcohol, formalin and boiling)
- Both diseases produce clostridium toxins

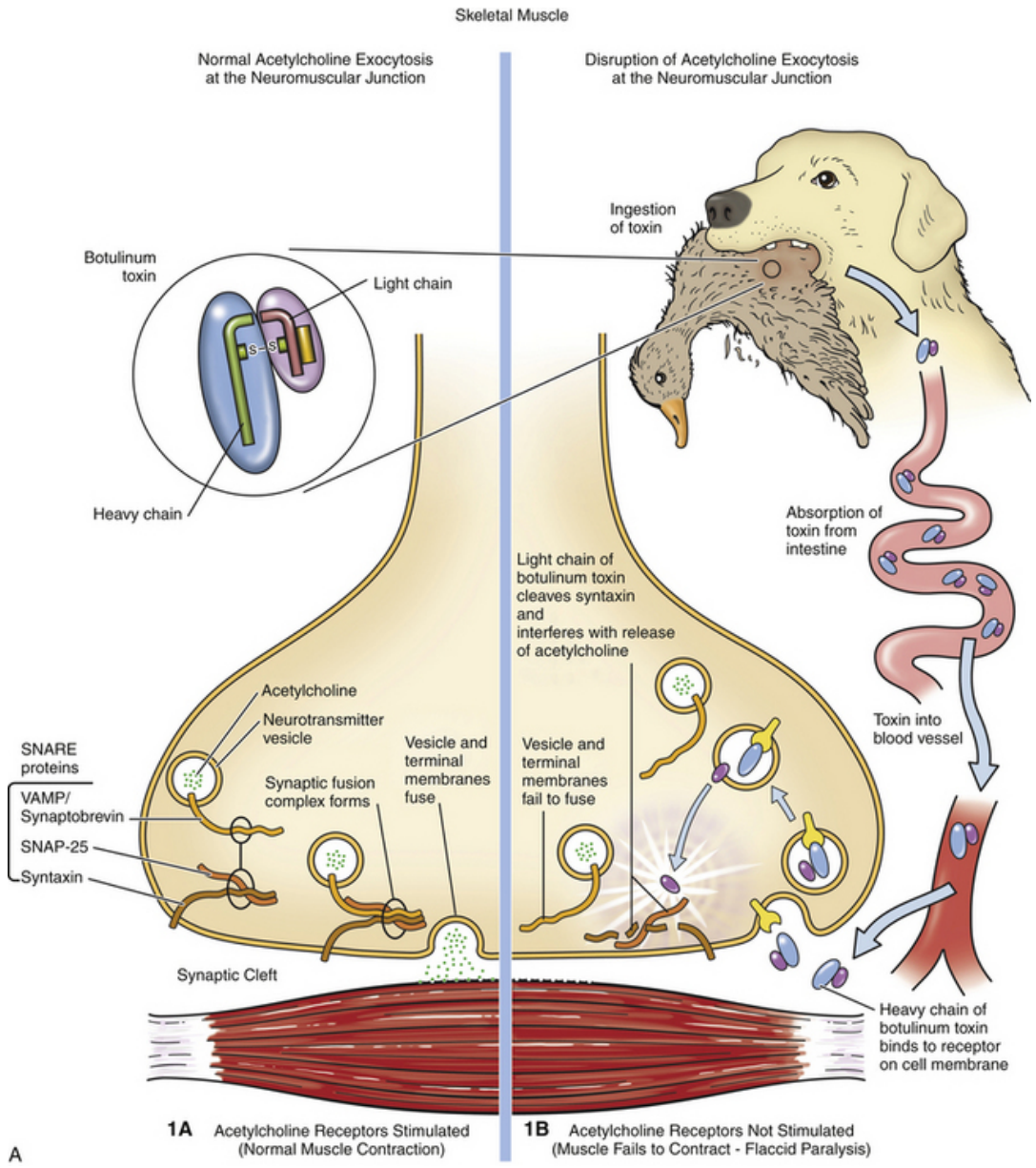
CLOSTRIDIUM TOXINS

- **don’t need to know this level of detail (toxin structure) for boards**
- Potent toxins
- Contains 2 polypeptide chains: heavy (H) and light (L) chains held by disulfide bonds
- H chain attaches to presynaptic nerve terminal membrane receptors → internalized via receptor-mediated endocytosis into presynaptic nerve terminal
  - Once in nerve terminal they act on separate targets
- L chain is a zinc-dependent MMP
  - Released from synaptic vesicle and cleaves docking proteins → inactivates NTM release
  - Docking proteins are critical for release of NTM from synaptic vesicles into synaptic clefts



BOTULISM

- Clostridium botulinum
- Transmitted via ingestion of preformed toxin (Decaying carcasses, vegetable materials)
- Medium-large breed, intact male/females, outdoor roaming pets
- Several toxins (A-F); botulism in dogs and cat caused by **toxin C (BoNT/C)**
- Onset of sign within 12-72h following ingestion
- Cx; Flaccid muscle paralysis – rapid, progressive, symmetric ascending LMN paresis without sensory deficits
  - +/- Parasympathetic symptoms, megaesophagus
  - Death due to respiratory or cardiac paralysis



BOTULISM

- Botulinum toxin is ingested → binds receptors on gastric and small intestine ep cells → absorption via endocytosis
- Absorbed toxin is carried via bloodstream to peripheral nerve cells
  - H chain binds to receptors on presynaptic nerve terminal → prevent fusion of ACh-containing synaptic vesicle from fusing at terminal
  - L chains cleaves syntaxin and interferes with ACh release
- Lack of ACh = lack of muscle contraction = paralysis

BOTULISM

- Diagnosis: History + PE, EMG, detection of BoNT (ELISA [toxin or Ab], electrochemiluminescence detection, or mouse inoculation bioassay*)
  - Electrophysiological studies support diagnosis (decr amplitude of cMAP, reduced nerve conduction velocity)
  - Usually by the time signs appear, toxin is no longer detectable in blood → need serum titers
- Treatment is supportive
  - Recumbent care
  - ABX: Penicillin or metronidazole
  - +/- mechanical ventilation
- Botulinum antitoxin: Neutralize unbound BoNT
- Most die within 24 hours
- Recovery can take 1-3 weeks, but residual signs can persist for months

TETANUS

- Clostridium tetani
  - Soil and feces of animals
- 3 toxins: **Tetanospasmin** (neurotoxin), tetanolysin (hemolysin, insignificant), nonspasmogenic toxin (unclear role)
- Introduction of spores via penetrating wound into dogs and cats
  - However up to 1/3 of dogs have no known wound history (cryptogenic tetanus)
  - E.g. traumatic wounds, draining tracts associated with plant material, tick bites, surgical wounds etc
- Young, large-breed, active outdoor dogs or young outdoor cats
  - Cats more resistant to disease
- Death occurs occ. in dogs but rarely in cats

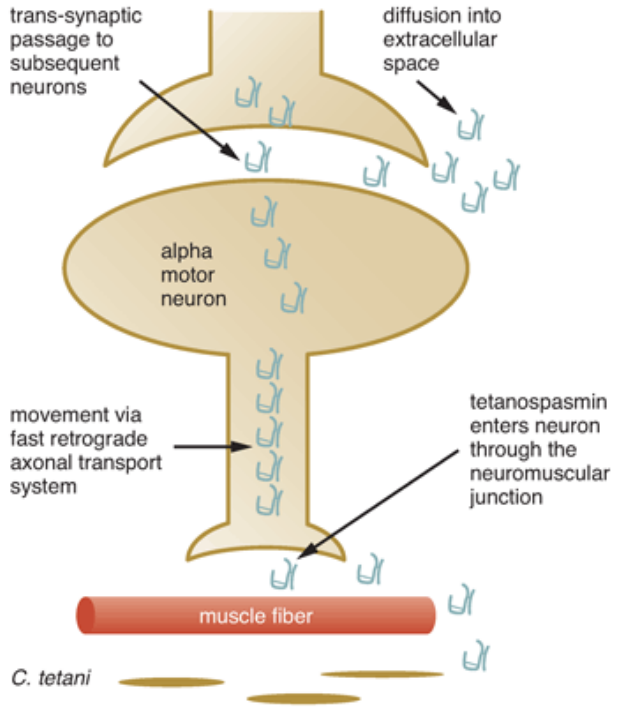
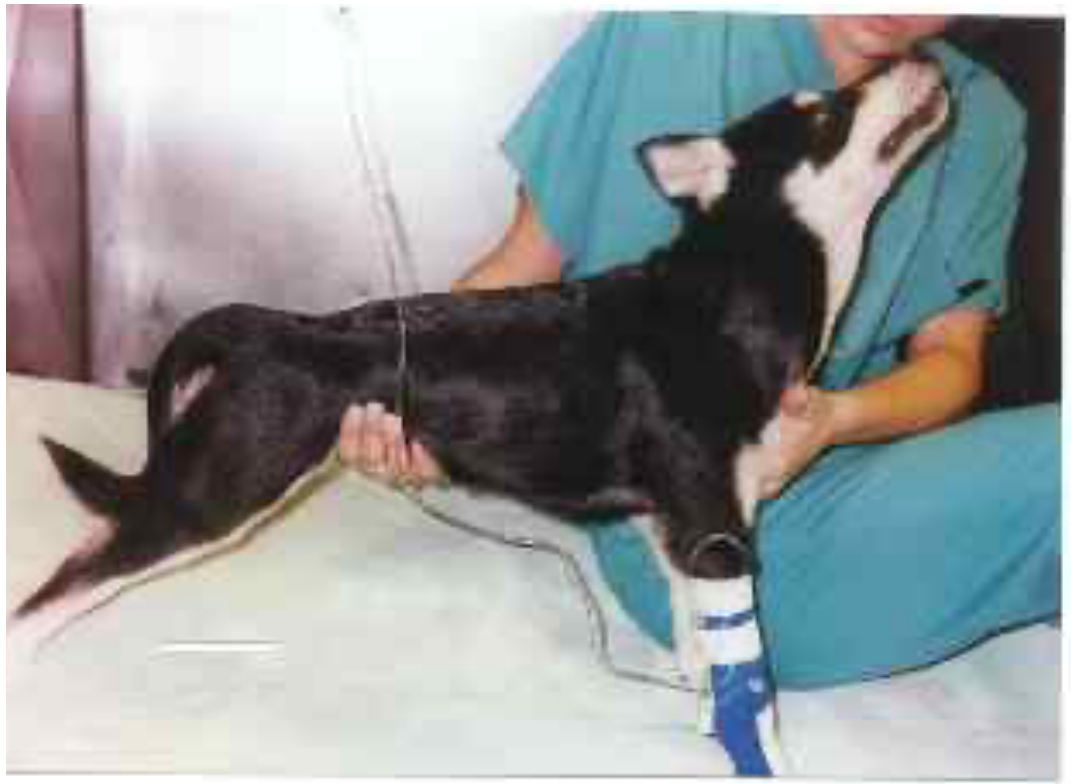


FIGURE 37.13 Tetanospasmin diffuses from the site of introduction to the alpha motor neuromuscular junction. It moves via the retrograde transport system to the cell body, from which it diffuses out into the synapses and extracellular space within the spinal cord or brainstem.

TETANUS

- Tetanospasmin diffuse from wound → hematogenous spread
  - Binds to presynaptic terminals of LMN → internalized → retrograde travel up axons and enter inhibitory interneurons in the spinal cord or brain
  - interferes with the release of GABA and glycine (inhibitory NTMs)
  - Results in unhindered excitation of motor neurons, spastic paralysis, and dysfunction of SNS and PNS
- Tetanolysin causes hemolysis and enhances multiplication of anaerobic bacteria (increases tissue necrosis)

TETANUS



- Incubation period around 5-10 days
  - Shorter onset if wound closer to CNS or if large amount of toxins are present
- Cx: Spastic paralysis with sawhorse stance and facial grimace (risus sardonicus)
  - Exaggerated reflex, hyperesthetic, opisthotonus, erected ears, seizure when stimulated, hyperthermic
  - Hiatal hernia possible
- Death occurs in severely affected pets with respiratory muscle paralysis
- In cats, usually localized to one limb

TETANUS

- Diagnosis usually made based on Cx
  - Elevated CK
  - Isolation of C. tetani is difficult – requires special culture media (slow growing, takes 12d), may be able to see g+ve rods
- Treatment: IV antitoxin, ABX (penicillin/metro), wound care, sedative/muscle relaxants, supportive care
  - ABX indicated to eliminate vegetative C. tetani and to prevent further toxin formation
  - Antitoxin given ASAP following onset of Cx
    - Doesn’t hasten recovery as bound toxin is cleared slowly

QUESTION

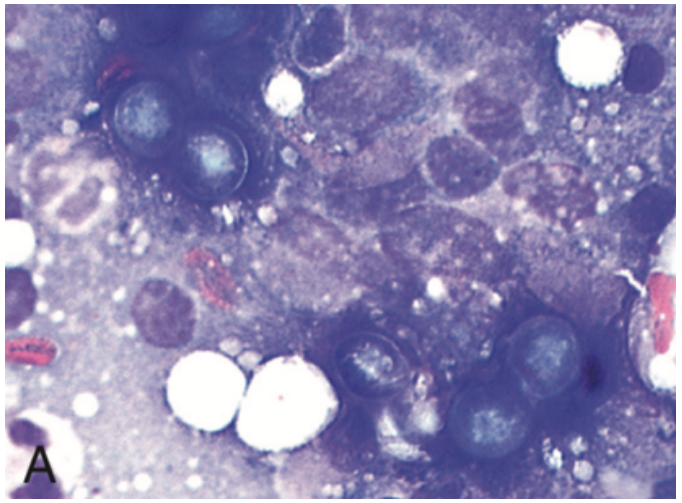
- Which toxin causes Botulism?
- Mechanism by which a pet gets botulism vs tetanus?
- What NTMs does tetanospasmin inhibit the release of?

FUNGAL INFECTIONS

BLASTOMYCOSIS

- Blastomyces dermatitidis
  - Moist, acidic soil with decaying vegetation/animal feces
  - Mississippi, Missouri, Ohio river valleys, great lakes
- Route of transmission: Inhalation or percutaneous inoculation by conidiophores
- Dogs > cats
- Following inoculation, infective conidia are phagocytosed by macrophages → transformed to thick-walled yeast phase → bud to form daughter cells with broad-based attachments
- Onset of signs: Weeks to months

BLASTOMYCOSIS



- Cx: Anorexia, lethargy, depression, weight loss, fever
  - Lymphadenomegaly, respiratory signs, ocular (uveitis, retinal detachment, glaucoma), dermal nodules, bone lesions, CNS signs
- Diagnosis:
  - TXR: Diffuse or nodular interstitial pattern, alveolar infiltrates, hilar lymphadenopathy
  - Bone: Periosteal proliferation, soft tissue swelling on appendicular skeleton
  - Cytology: Thick-walled, budding organism from affected tissue
  - Serology: agar del immunodiffusion (AGID) Sn 41-90% Sp 90-100%
    - Often negative early in the course of disease, may remain positive even if there is clinical resolution
  - MiraVista urine or serum antigen (urine Sn 87%, serum 93%), low rate of false +ve in uninfected dogs , detects cell surface glycoprotein BAD-1
  - Dogs with systemic blasto are more hypercoagulable than normal dogs (McMichael JVIM 2015)
  - Ionized hypercalcemia with lower 25(OH)D and PTH levels; not related to survival (O'Brien JVIM 2018)

BLASTOMYCOSIS

- Treatment:
  - Azole antifungals: Itraconazole
  - No published benefit of anti-inflammatory (NSAID vs corticosteroid) on 30 day survival (Walton JVECC 2017)
- Prognosis good unless pulmonary or CNS involvement. Overall 70-75% survival
  - If resp infection or multiple body system involved = more likely to die within 1st week
  - If severe dz and elevated band neutrophils = poor prognostic indicator
  - Many dies during or soon after tx due to inflammatory response associate with sudden death of fungal organisms
  - O2 supplementation associated with decreased survival

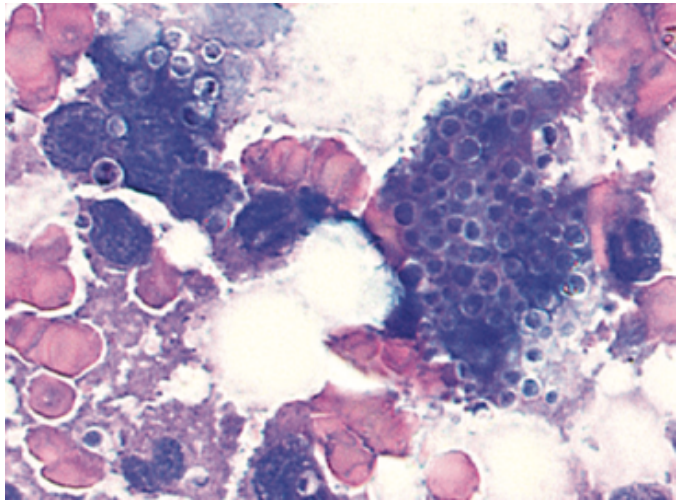
HISTOPLASMOSIS

- Histoplasma capsulatum
  - Soil containing bat or bird waste containing free-living microconidia or macroconidia
  - Ohio, Missouri, Mississippi river valleys
- Route of transmission: Respiratory > oral
- Microconidia is inhaled → transform into unicellular yeast in lungs → phagocytosed by macrophages + replicate intracellular
  - Disseminate systemically: Lungs, GIT, spleen, liver, bone marrow, eyes, adrenal glands
- Incubation period: 1-2 weeks

HISTOPLASMOSIS

- Dogs: Male large breed, young-adult, hunting breeds
  - GI signs most common: diarrhea +/- hematochezia, melena, weight loss, hypoalbuminemia
  - Rarely pulmonary , bone, ocular or dermal lesions
- Cats: Older female cats
  - Weakness, lymphadenomegaly, weight loss, anorexia, lameness/joint effusion
  - Less commonly present with primary GI signs
  - Bone marrow, ocular, urinary and dermal lesions seen

HISTOPLASMOSIS



Diagnosis

- CBC: nonregenerative anemia (chronic inflammation), thrombocytopenia
  - Hemophagocytosis can be seen in cats (Schaefer vet clin path 2019)
- Chem: hypoalbuminemia, ELE, bilirubinemia, hypercalcemia
- TXR: diffuse or nodule interstitial infiltrates, hilar lymphadenopathy
- Definitive dx: Cytology or histopathology
  - Organisms found clustered in mononuclear phagocytes - thin, clear halo surrounding basophilic cytoplasm
  - Samples obtained from affected tissue (Mucosal scraps, FNA liver/spleen/LN/skin lesions, joint effusion)
- Serology: false -ve occur in active disease and false +ve occur in animals without active disease (AGID, MiraVista Ag)
  - Can cross react with Blasto for Ag test

HISTOPLASMOSIS

- Treatment: Itraconazole
- Prognosis: Guarded to good depending on nature of disease
  - Negative prognostic indicators in cats: Severe respiratory dz, hepatic, hematologic or neurological dz
  - Negative prognostic indicators in dogs: Great Pyrenees, dyspnea, need for O2, icteric, organomegaly, anemia, thrombocytopenia, hypercalcemia, elevated ALP and hyperbilirubinemia (Wilson JAVMA 2018)

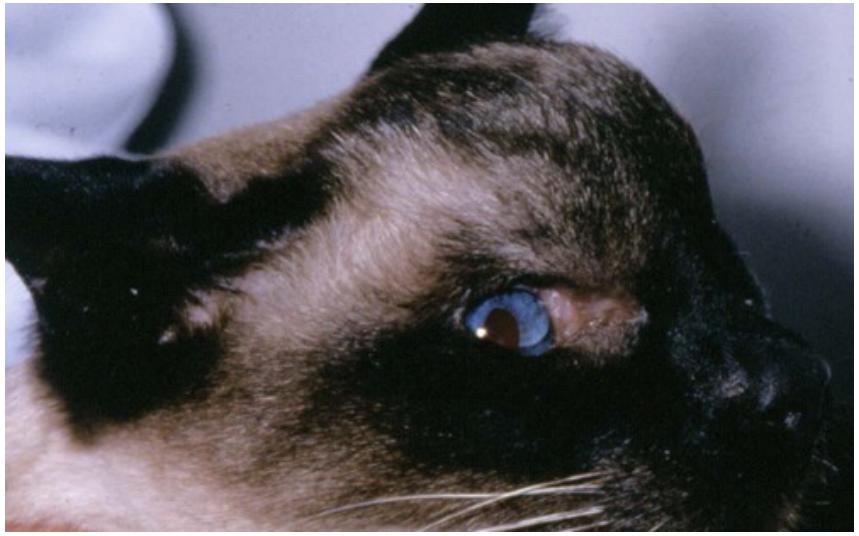
CRYPTOCOCCOSIS

- Cryptococcus neoformans and gattii
  - Saprophytic, round, yeast-like fungus, capsule
  - Reproduce by budding from the parent cells
  - Sources: avian habitats (*C. neoformans*) or hollows of eucalyptus trees (*C. gattii*)
- Cats 5-6x more likely to be affected than dogs
- Route of transmission: Inhalation >>> wound inoculation
- Unencapsulated basidiospores are inhaled from the environment → Deposit into tissue and colonize the upper respiratory tract (rhinitis) and regain their capsules
  - Capsules prevent normal host immune response + elimination
  - CNS involvement is common, usually via extension from nasal cavity --> brain via ethmoid bone
- Incubation period: Months to years

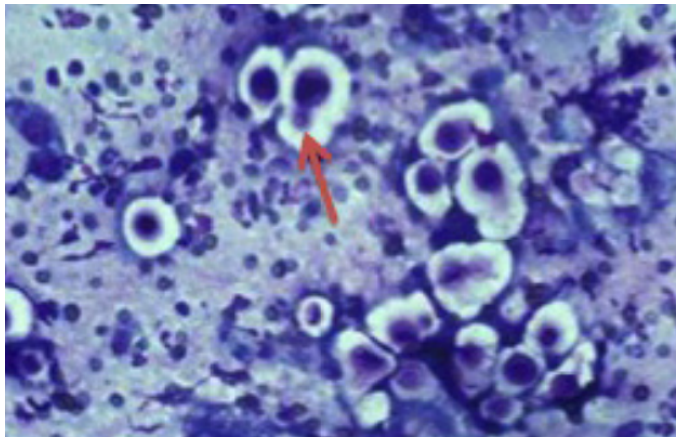
CRYPTOCOCCOSIS

Clinical signs

- Cats:
  - Ragdoll, Birmans, Siamese, Himalayans
  - URI in 50-60%, presence of ”Roman nose”, glistening, serosanguinous gelatinous mass, nasal discharge, ulcerative skin lesions
  - Chronic mucosal lesions in the nasal cavity
  - Ocular + CNS signs in 15%: Blindness (retinal detachment, granulomatous chorioretinitis), neurological signs (depression, temperament change, ataxia, vestibular signs)
  - Cutaneous and systemic forms less common
  - Can see ocular + CNS signs without ”roman nose” as well
- Dogs:
  - Usually <4 years old
  - Breeds: Great Danes, Dobies, Labs, American Cockers
  - >80% have > 1 site affected: CNS and ocular



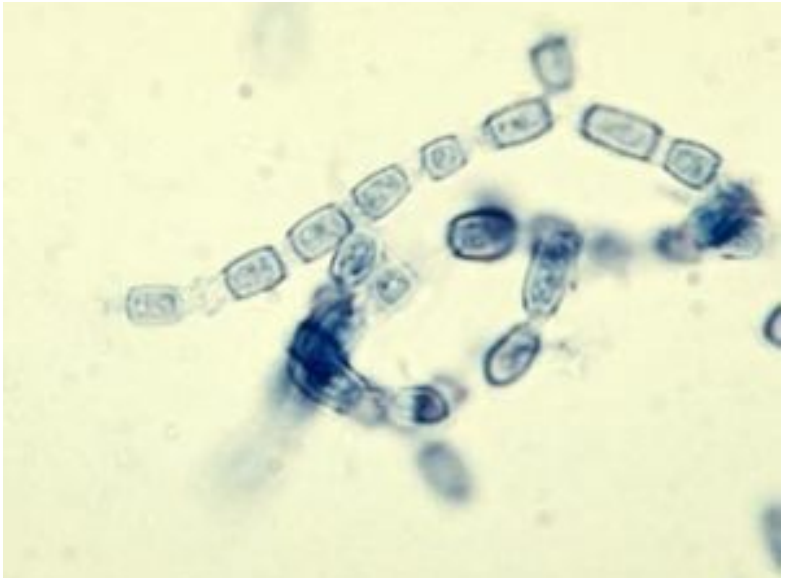
CRYPTOCOCCOSIS

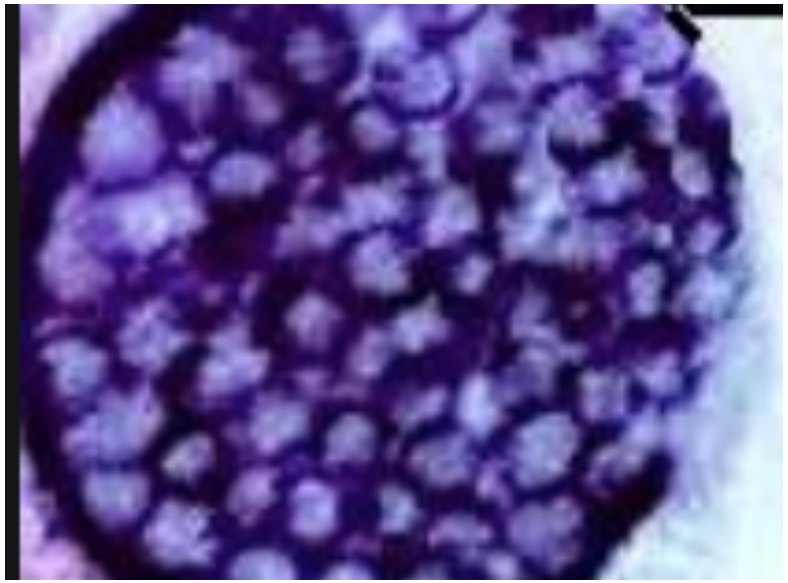


- Diagnosis
  - Skull rads may show nasal bone destruction and soft tissue swelling
  - Detect Crypto Ag from lesions or bodily fluids: PCR, LCAT
  - Cytology to visualize Cryptococcus = easily performed with Diff Quik
  - Consider culture if Ag test is negative
  - Serologic testing can be used to aid dx
    - Latex agglutination to identify capsule antigen, positive at titer $\geq$1:16
- Treatment: Fluconazole (some resistance reported with C. gatti)
  - Ideally tx until 1-month past resolution of signs, decr in Ag titers by 2-fold, or until results are negative
- Prognosis: Good in cats without CNS penetration; guarded to poor in dogs

COCCIDIOIDOMYCOSIS (VALLEY FEVER)

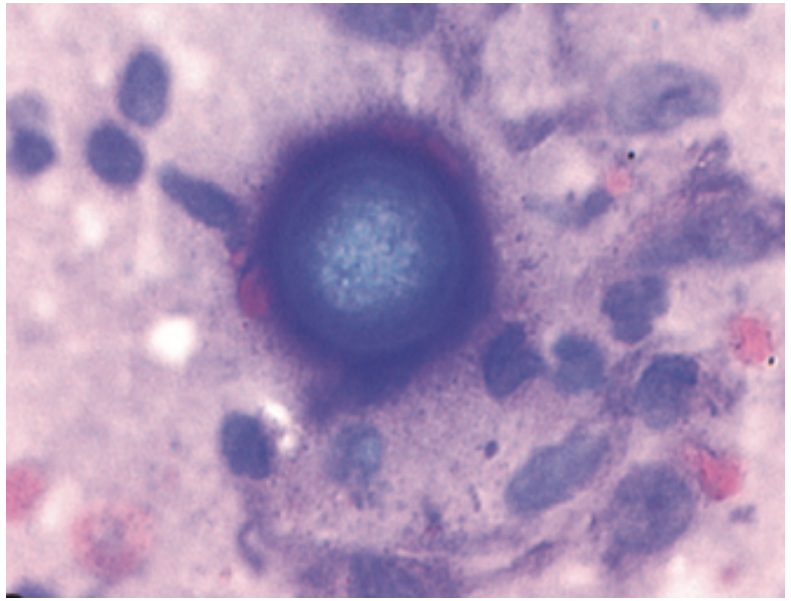
- Coccidioides immitis
  - Soil saprophyte, grows on semiarid condition
  - Endemic to Southwestern US, Mexico, Central and South America
- Route of transmission: Inhalation
- Zoonotic
- Arthoconidia are inhaled → Migrate through pleural tissue to subpleural space → Phagocytosed by macrophages → Transform into spherules in alveoli and develop hundreds of endospores
- Endospores rupture once release, each creating a new spherule to perpetuate infection
  - Peripheral lymphadenomegaly occurs 1st then the spherules disseminate
- Incubation period: 1-3 weeks
  - Can remain dormant for 3 years prior to Cx

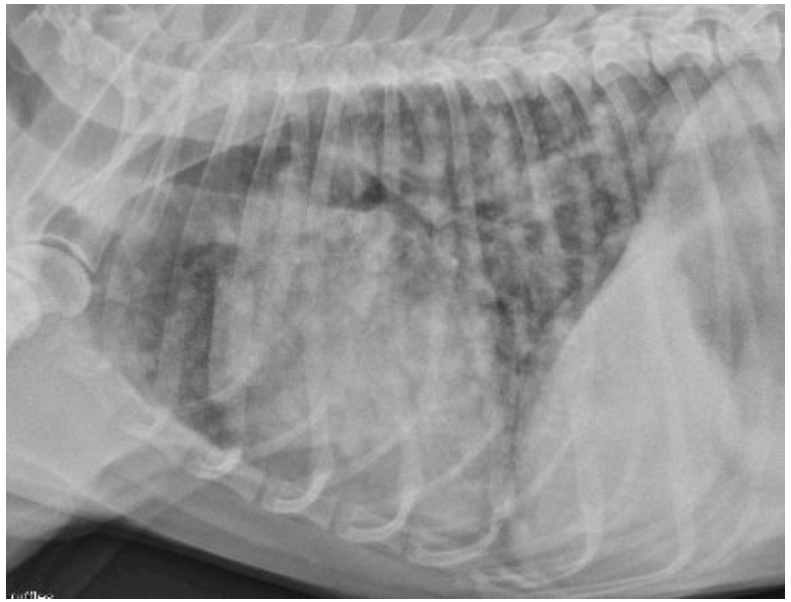




COCCIDIOIDOMYCOSIS (VALLEY FEVER)

- Cx: Develops intense inflammatory response → respiratory, neurologic, cardiac, cutaneous and ocular presentations
  - Chronic cough is the most common presenting sign
  - 20-42% of dogs have disseminated disease
  - Immune complex GN possible (Mehrkens JVIM 2016)
  - Intracranial form presents with seizures; Schnauzers may be predisposed (Spoor JVetRadUS 2018)
- Cats are more resistant to infections than dogs
  - Usually have cutaneous manifestations





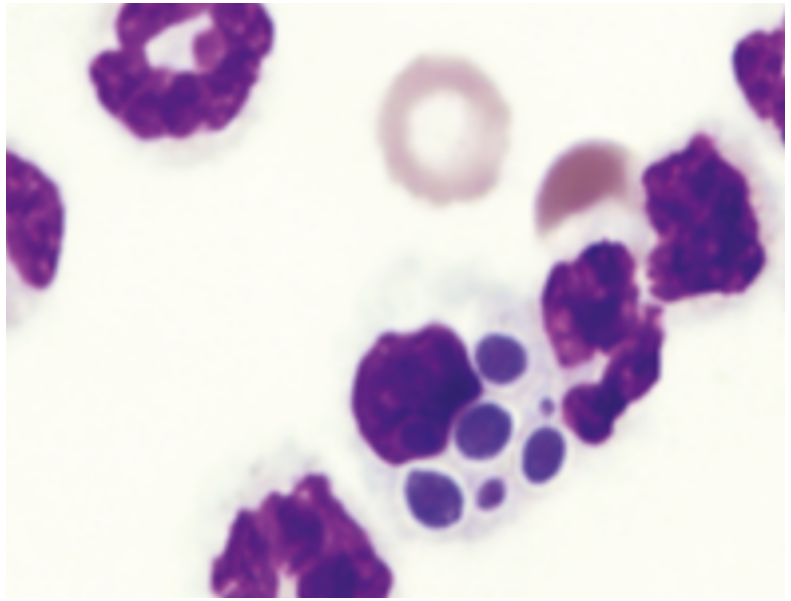
COCCIDIOIDOMYCOSIS (VALLEY FEVER)

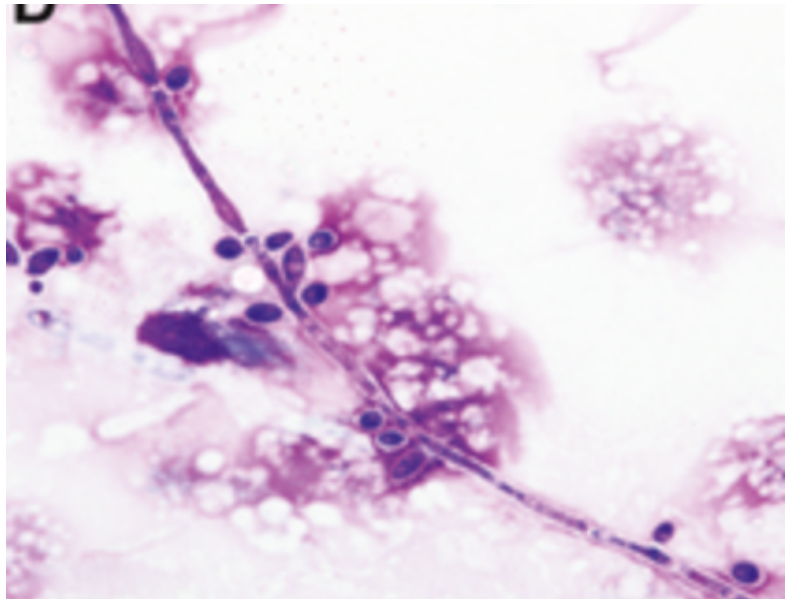
Diagnosis:

- CBC: Normocytic normochromic nonregenerative anemia, neutrophilia with left-shift and monocytosis
- Chem: Hypoalbuminemia and hyperglobulinemia, ELE, possible hypercalcemia
- TXR: Diffuse interstitial/peribronchial/alveolar infiltrates with sternal lymphadenopathy
- MRI: Focal unilateral granuloma or bilaterally symmetric T2 hyperintensity with extensive vasogenic edema
- Cytology is insensitive – may see mycelium with thick-walled, barrel shaped arthroconidia
  - Localizing organisms often difficult as spherules are low in # and endospores are phagocytosed
  - Can often be found in CSF, however
- Serology: Most commonly used as screening test
  - Sensitivity 87% for IgG and 46% for IgM
  - Obtain convalescent titers in –4 weeks to demonstrate increasing titers = confirm diagnosis

COCCIDIOIDOMYCOSIS (VALLEY FEVER)

- Treatment: Difficult to cure compared to other fungal infection, requires life-long treatment
  - Azole anti-fungal superior to amphotericin B, esp if CNS involvement
  - Requires repeat serologic testing in 4-6 weeks to monitor response
  - Relapse is common following discontinuation of tx
- Prognosis
  - Disseminated infection result in death if untreated
  - CNS involvement = worse prognosis
  - Overall 60% recovery with ketoconazole





CANDIDIASIS

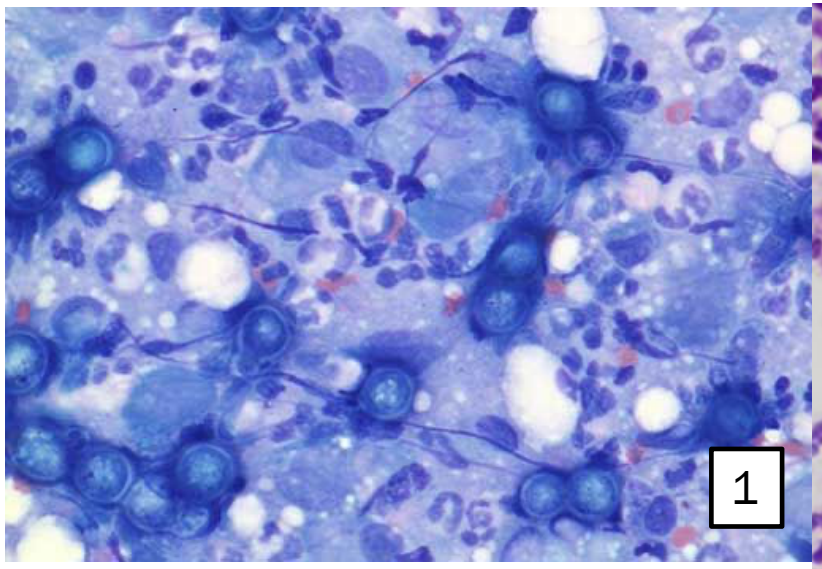
- *Candida albicans* >> *Candida glabrata*
  - Deeply basophilic yeast with clear capsules
  - Dimorphic: Pseudomycelium (non-septate) and chlamydoconidia (thick-wall sphere) forms possible
  - Commensal of mucosal surfaces (esp. GIT, urogenital tract)
- Route of transmission: Endogenous
- Immunosuppression is a major predisposing factor
  - Normally neutrophil phagocytosis resolves overgrowth
- During pathologic state, Candida reacts with host immune system → undergoes phenotypic switch from blastoconidia yeast form to a more resistant germ tube or elongated yeast (pseudohyphae and true hyphae)

CANDIDIASIS

- Cx signs: Nosocomial UTIs, peritonitis, cutaneous + mucocutaneous infections, GI overgrowth, ulcerative glossitis, keratitis, arthritis all possible
  - Most common manifestation is candiduria in dogs
- Risk factors for candiduria in dogs: Recent (30d) administration of antimicrobials, immunosuppression in dogs, and lower urinary tract disease (dogs only) (Reagen JVIM 2019)
- Candida peritonitis occurred in dogs with hx of antimicrobial administration coupled with recent GI/biliary sx or NSAID-induced intestinal ulceration (Bradford, Vet Clin Path 2013)
  - All cases diagnosed via cytologic evaluation of peritoneal effusion
- Other reported risk factors: DM, presence of catheters (U-cath, central lines), glucocorticoid administration, TPN

CANDIDIASIS

- Diagnosis
  - Cytology from tissue, bodily fluids or skin scrap (gram, methylene blue or Wrights stain)
  - Fungal culture
- Treatment: Fluconazole (systemic); clotrimazole or nystatin (topical)
- Prognosis: UTIs = okay, otherwise guarded/poor – usually associated with underlying condition (bacterial sepsis)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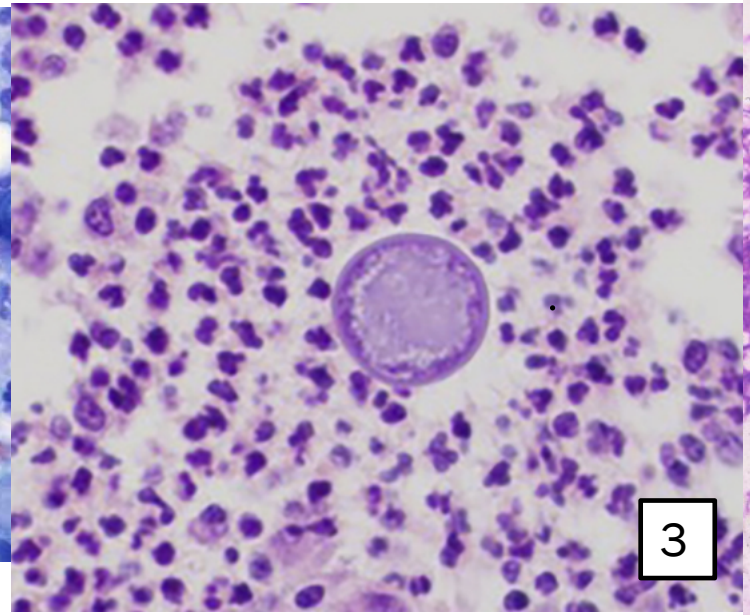
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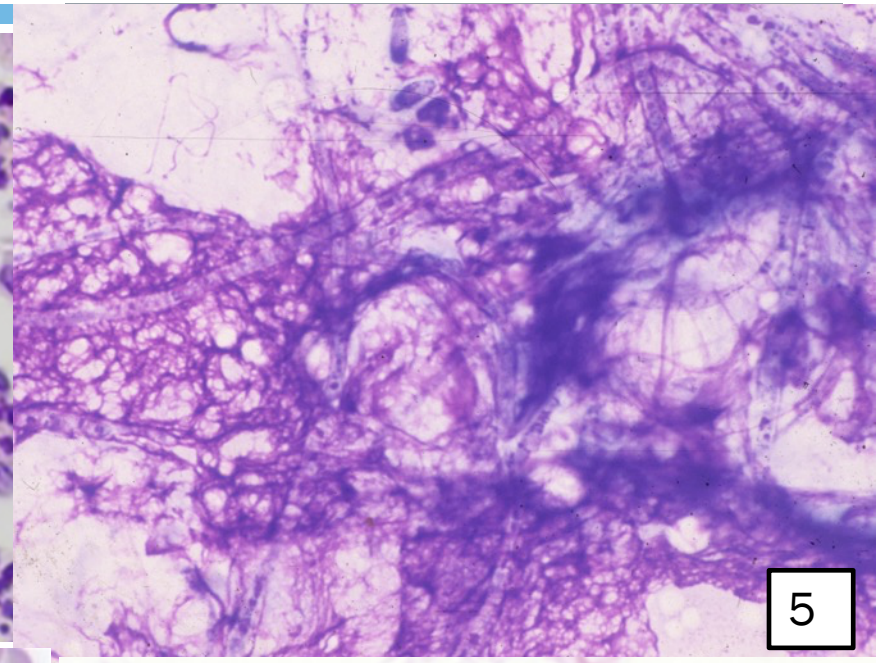
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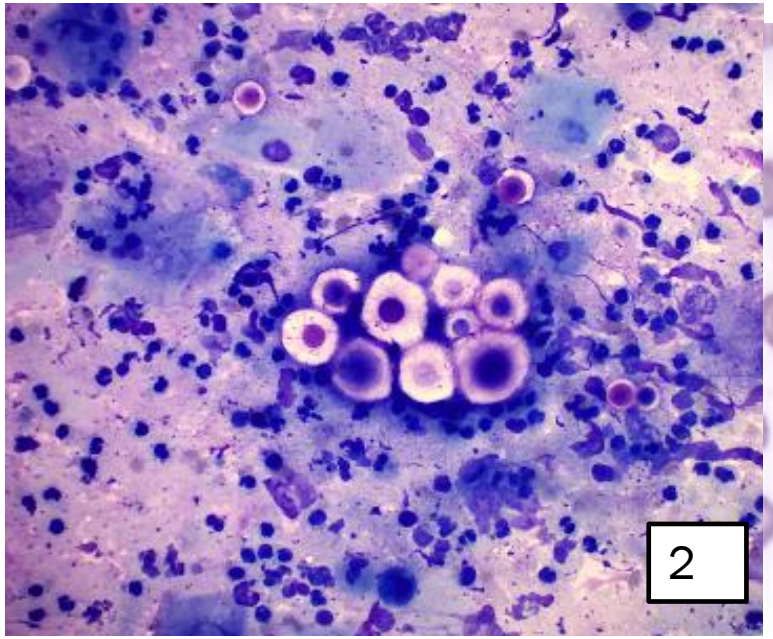
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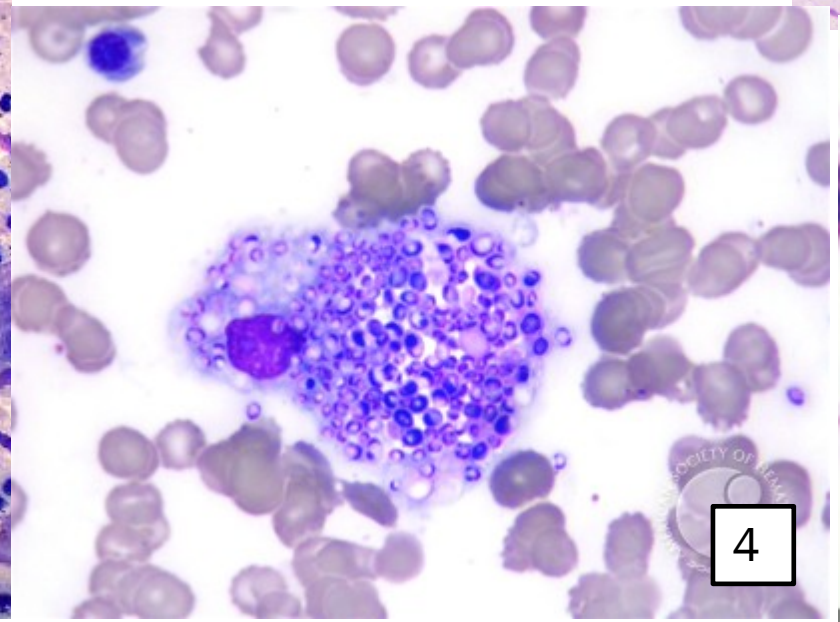
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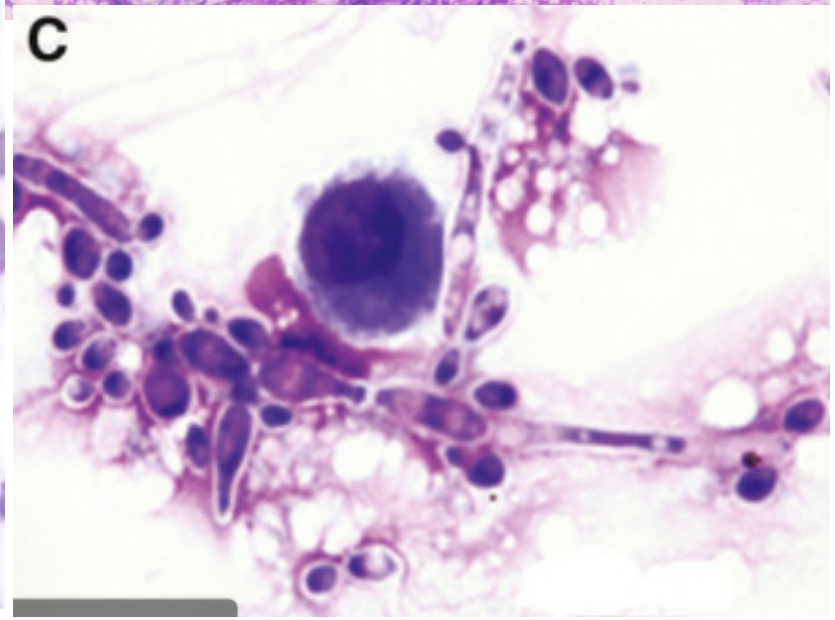
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THANKS!


I GOT A FUNGAL INFECTION ONCE
AND I WAS ON ANTIFUNGAL THERAPY FOR ONLY FORTY YEARS
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