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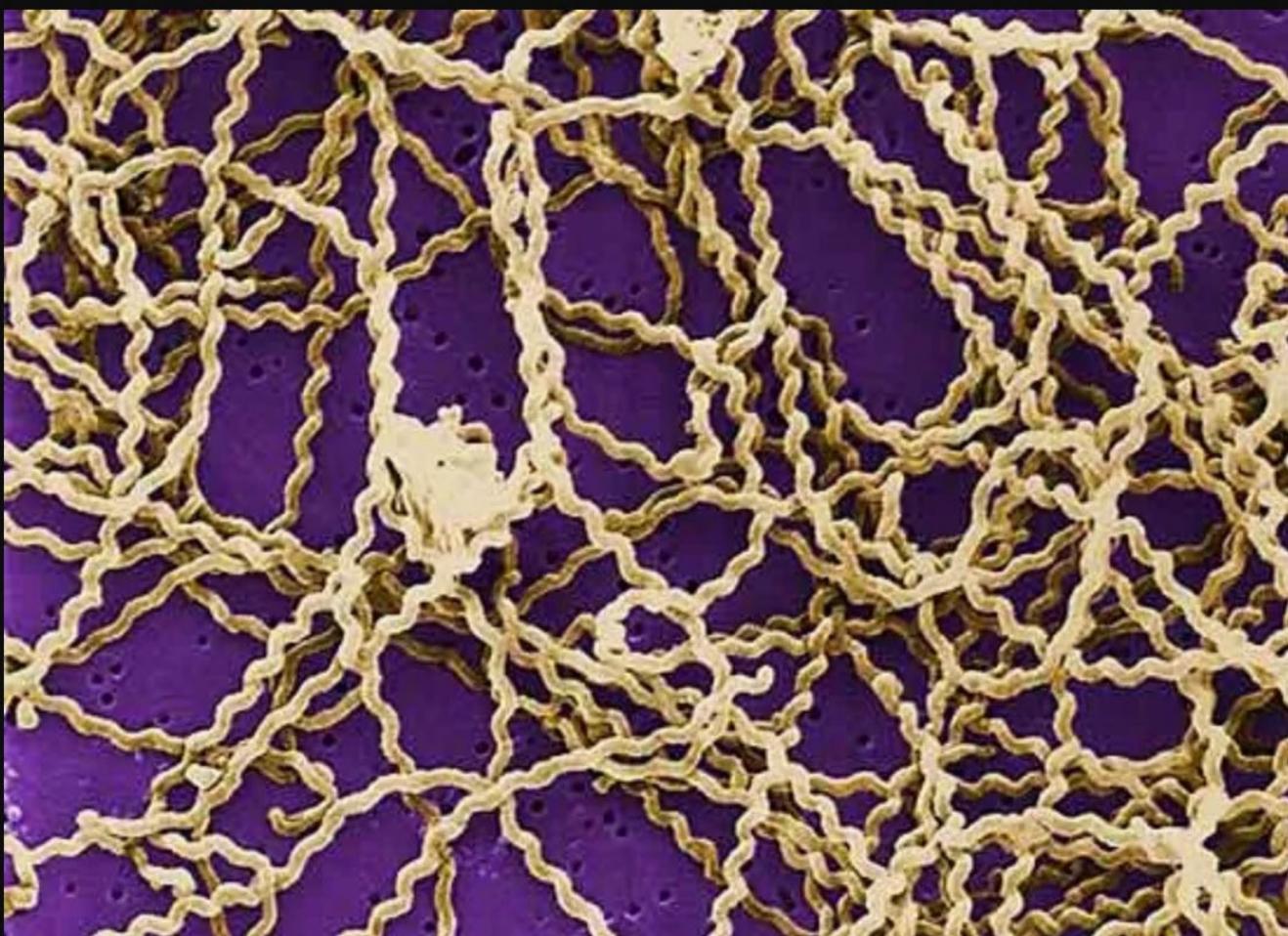
Leptospirosis

ASEC SYMPOSIUM
2024

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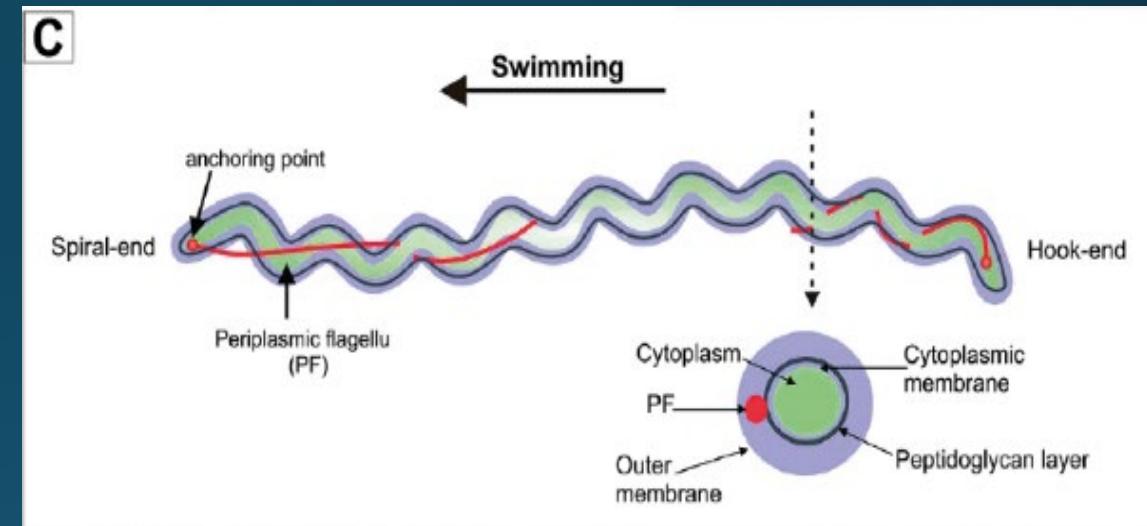
Outline

- Etiology
- Epidemiology
- Pathophysiology
- Diagnosis
- Treatment
- Prognosis
- Prevention



Etiology

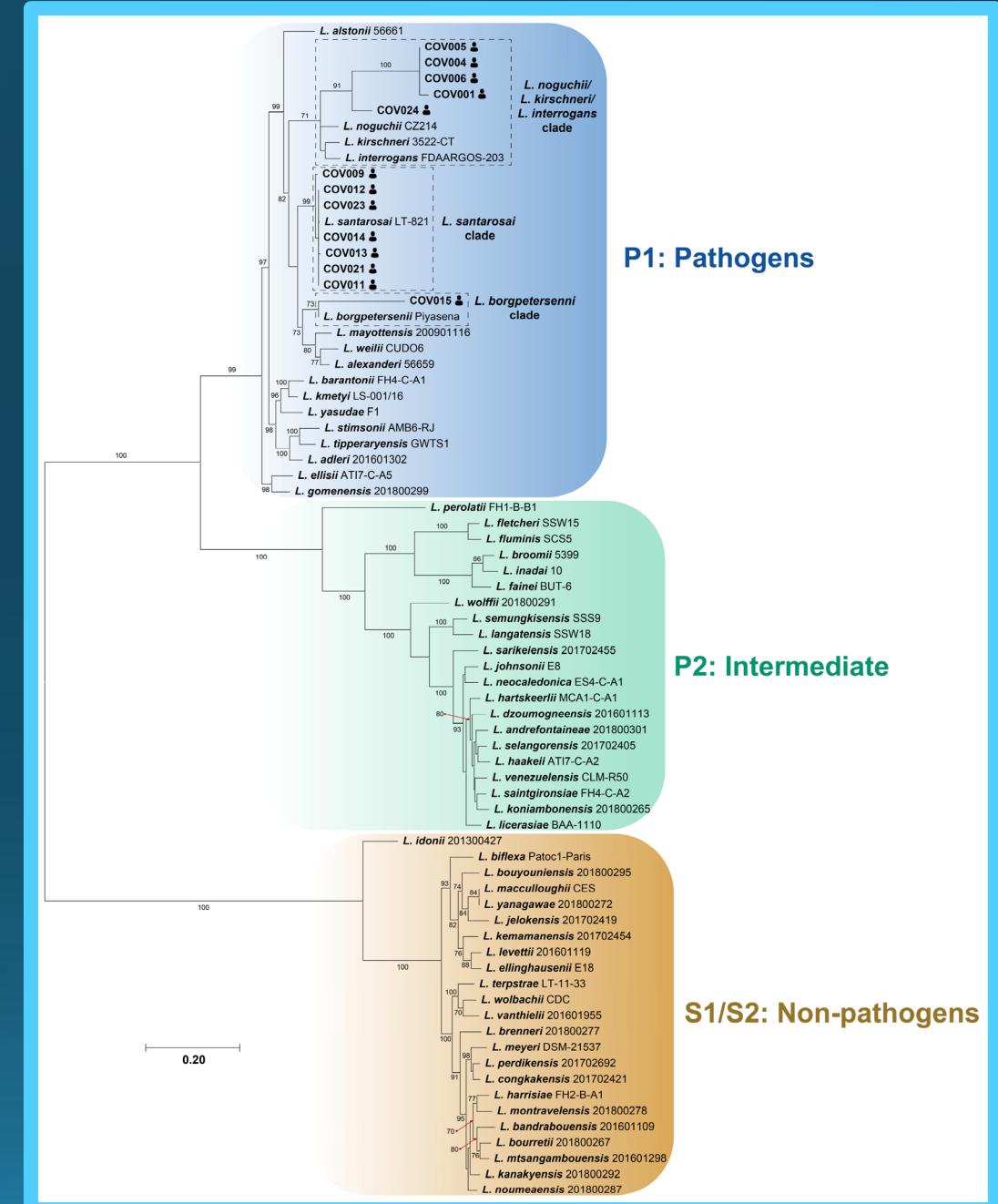
- *Leptospira* spp.
 - Spirochete bacteria
 - Leptos = “thin” ($0.1 \mu\text{m}$)
 - Spira = “coil”
 - Long (6-20 μm)
 - Gram-negative
 - Lipopolysaccharide (LPS) layer



DOI: 10.21521/mw.6694

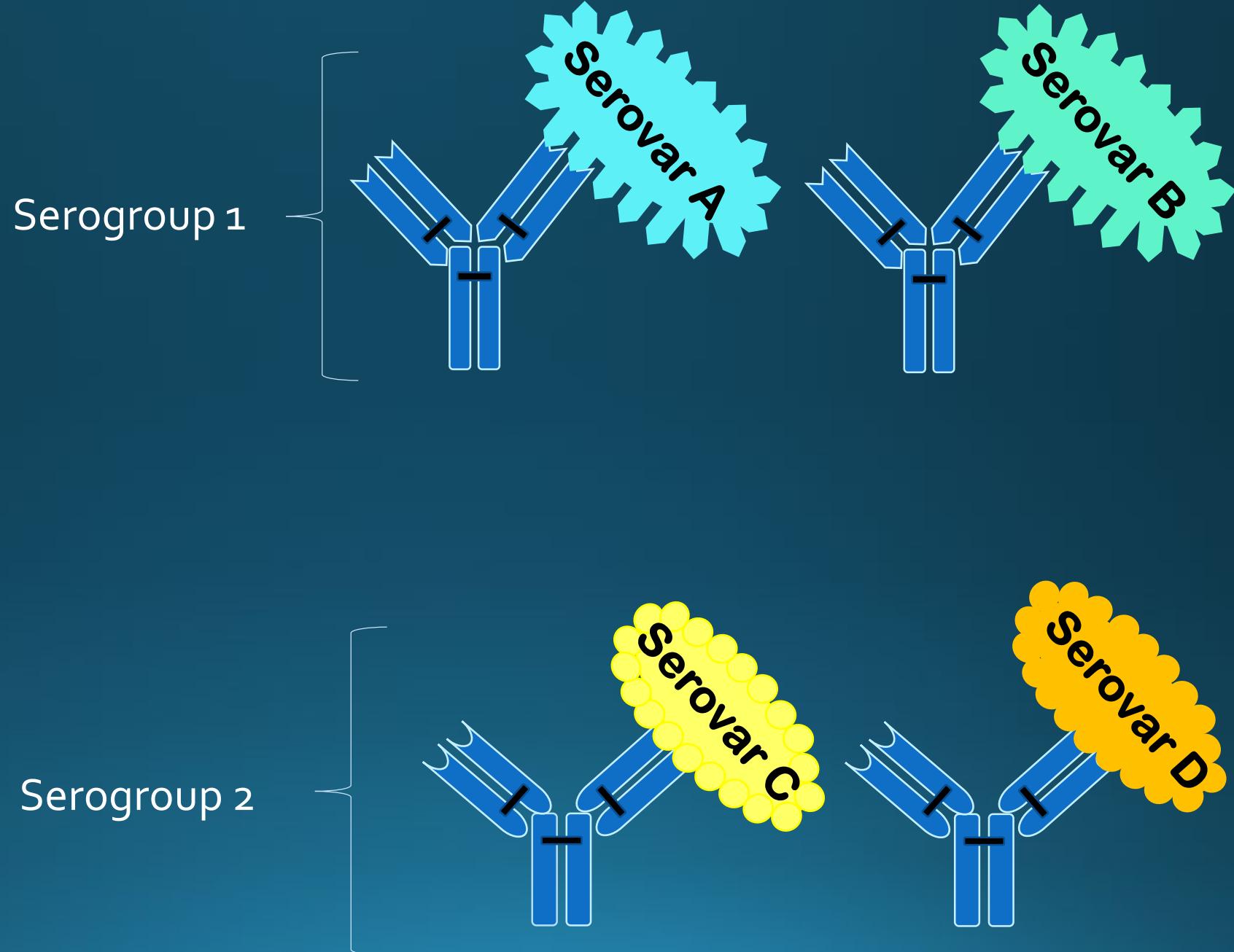
Etiology

- Pathogenicity
 - Pathogenic
 - Optimal growth at 28°C to 30°C
 - P₁ – High virulence
 - Most canine infections
 - P₁ – Low virulence
 - P₂ – Intermediate virulence
 - Saprophytic
 - Optimal growth at 11°C to 13°C
 - S₁/S₂



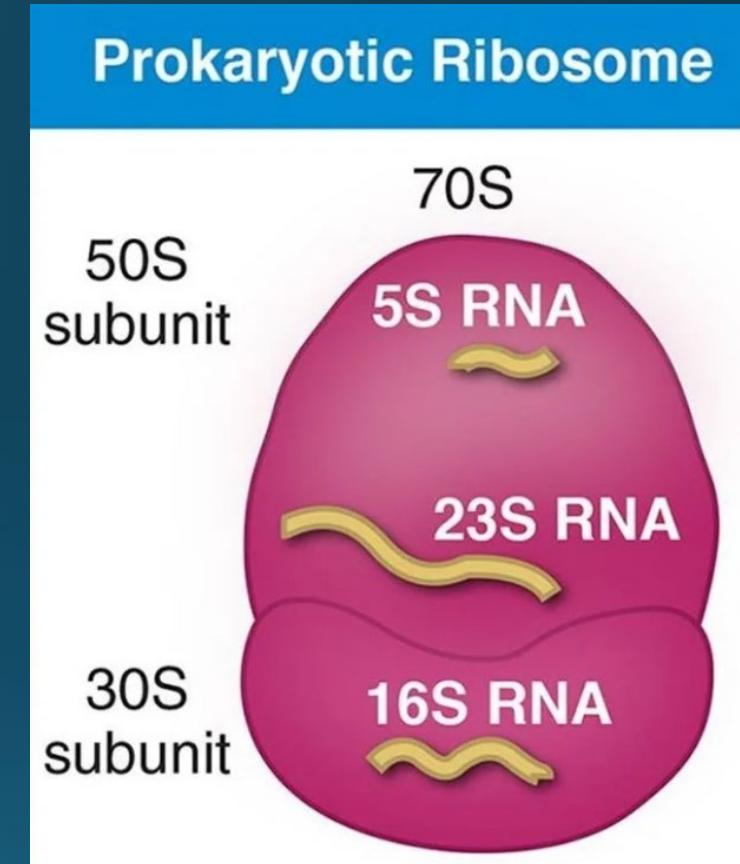
Etiology

- Serotyping
 - Serovars >300
 - Serogroups >25



Etiology

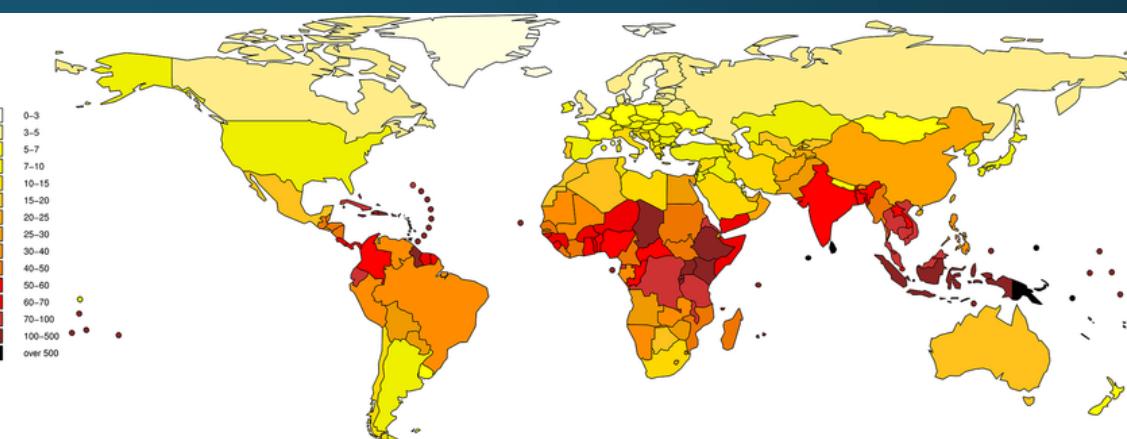
- Sequence types
 - 68 species based on 16S rRNA gene sequences



DOI: 10.1016/B978-0-12-816364-1.00002-0

Epidemiology

- **Incidental Hosts**
 - **Most mammals**
 - Humans
 - **Wildlife:** Wild bovidae, wild canids, rabbits, mice, rats, skunks, raccoons, armadillos, mongooses, voles, shrews, weasels, hedgehogs, otters, sea lions
 - **Domestic animals:** Cows, pigs, horses, sheep, goats, dogs*, cats
 - **Some birds, amphibians, reptiles, and fish**

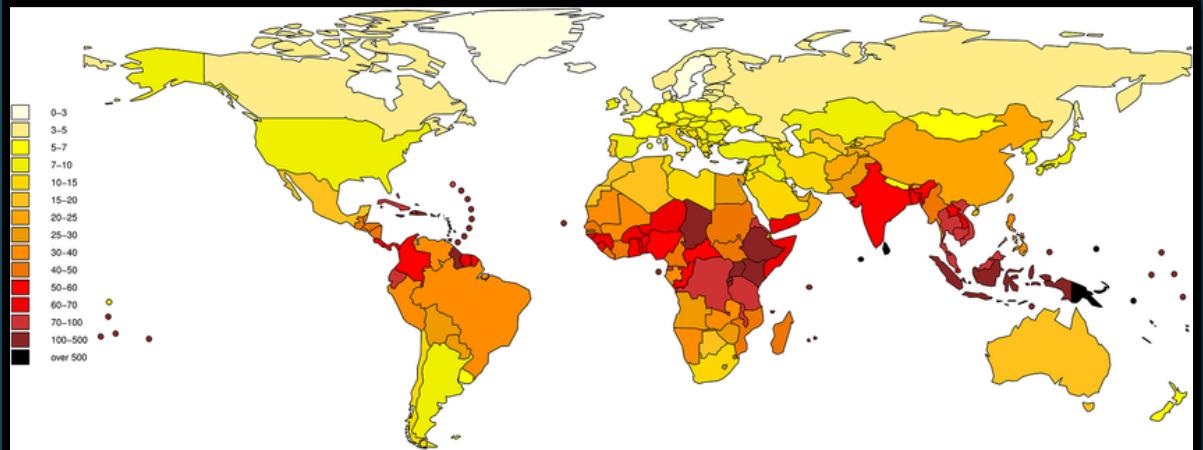


Serovar	Primary reservoir hosts	Incidental hosts
Hardjo	Cows	Dogs, humans, horses, pigs, sheeps, wild bovidae
Pomona	Cows, pigs, skunks, opossums	Dogs, cats, humans, horses, sheeps, goats, rabbits, mouses, raccoons, wolves, foxes
Canicola		Dogs, cats, humans, cows, horses, pigs, rats, raccoons, armadillos, mongooses, otters, skunks
Icterohaemorragiae	Rats Cats ?	Dogs, cats, humans, cows, horses, pigs, mouses, raccoons, opossums, foxes, woodchucks, skunks
Autumnalis	Mouses	Dogs, humans, cows, rats, raccoons, opossums
Bratislava	Rats, pigs, horses	Dogs, humans, cows, horses, mouses, foxes, voles, raccoons, opossums, skunks, weasels
Bataviae	Dogs, rats, mouses	Dogs, cats, humans, cows, hedgehogs, voles, armadillos, shrews

* Reprinted from Greene C, J Sykes, C Brown, K Hartmann. 2008. Leptospirosis. In: Greene C (ed). *Enfermedades infecciosas del perro y el gato*. Intermédica. Buenos Aires. Argentina. Copyright Elsevier.

Epidemiology

- Higher annual rainfall
- Warm climates
- Semi-arid climates
 - Dog Daycares in Los Angeles
- Higher rodent populations
 - Backyard poultry
 - Composting
 - Poor sanitation
- All dogs at risk

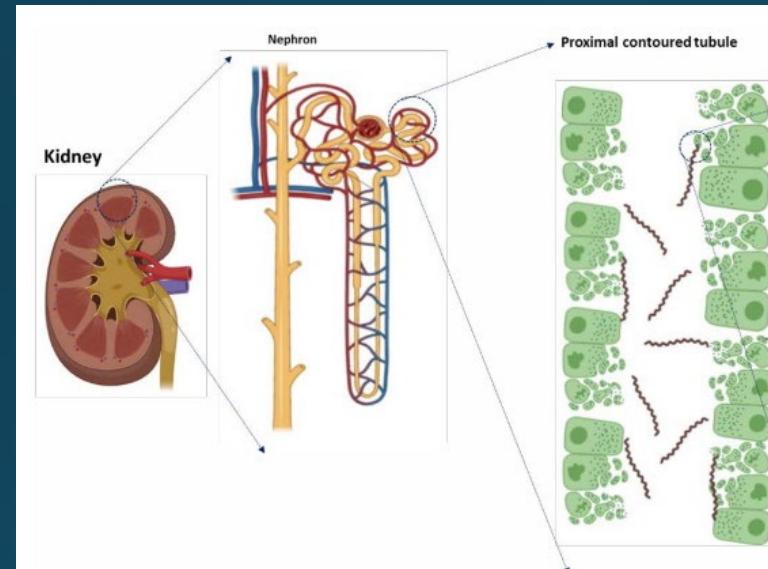


Pathophysiology

- Human infections
 - 3 to 30 day incubation period
 - Influenza-like illness
 - Weil's disease
 - Renal failure
 - Hepatic failure
 - Leptospirosis Pulmonary Hemorrhage Syndrome (LPHS)
 - Abortion or stillbirths
 - Transplacental infection



Pathophysiology: Transmission



- Predation
- Venereal
- Placental
- Transmammary
- Direct dog-to-dog?

Pathophysiology: Kinetics

- Incubation time
 - Humans: 3 to 30 days
 - Dogs: 2 to 20 days
- Leptospiremia
- Leptospiuria
 - One week after onset of illness
- Seroconversion
 - One week after onset of illness
 - Persists months to years
 - Delayed or absent in some
 - Blunted by antibiotic treatment

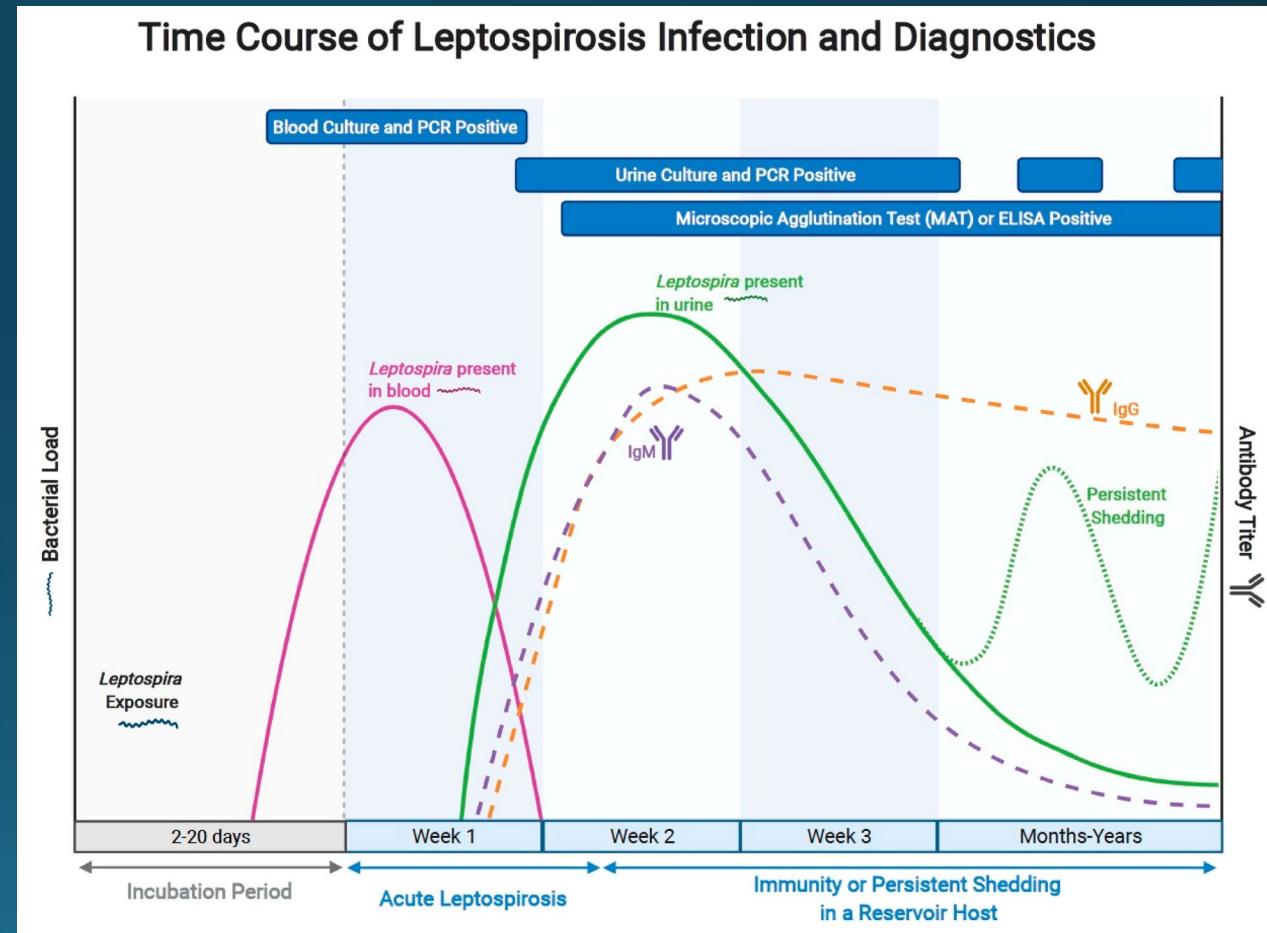


TABLE 1 Clinical manifestations of leptospirosis in dogs.

Organ involvement	Possible clinical signs	Diagnostic investigation
Acute kidney injury (tubulointerstitial nephritis)	Vomiting, diarrhea, dehydration, lethargy, inappetence, polyuria, polydipsia, oliguria, anuria, abdominal pain	Azotemia, electrolyte abnormalities, isosthenuria, glucosuria, proteinuria, pyuria, cylindruria, hyperechoic renal cortices
Cholestatic hepatopathy	Vomiting, diarrhea, dehydration, lethargy, inappetence, icterus	Increased liver enzymes, hyperbilirubinemia, hypoalbuminemia
Leptospiral pulmonary hemorrhage syndrome	Tachypnea, hemoptysis, increased breath sounds	Anemia, hypoxemia, diffuse or patchy interstitial to alveolar patterns
Coagulopathy	Petechiae, ecchymoses, hematuria, melena, hematemesis, epistaxis	Anemia, hypoalbuminemia, thrombocytopenia, hyperfibrinogenemia
Vasculitis	Peripheral edema, mild ascites, pleural effusion	Pleural effusion, mild ascites/retroperitoneal fluid
Pancreatitis	Vomiting, diarrhea, abdominal pain	Hyperbilirubinemia, increased liver enzyme activities, increased canine pancreas-specific lipase activity, increased DGGR lipase
Ocular involvement	Uveitis, conjunctivitis, retinal hemorrhages	Fundoscopic examination
Myocarditis	Cardiac arrhythmias	Increased serum troponin, ECG abnormalities
Enteritis	Vomiting, diarrhea, abdominal pain	Thickened intestinal walls, evidence of intestinal intussusception
Myositis	Reluctance to move	Increased CK activity
Reproductive tract	Abortion, infertility	
Skin	Calcinosis cutis	

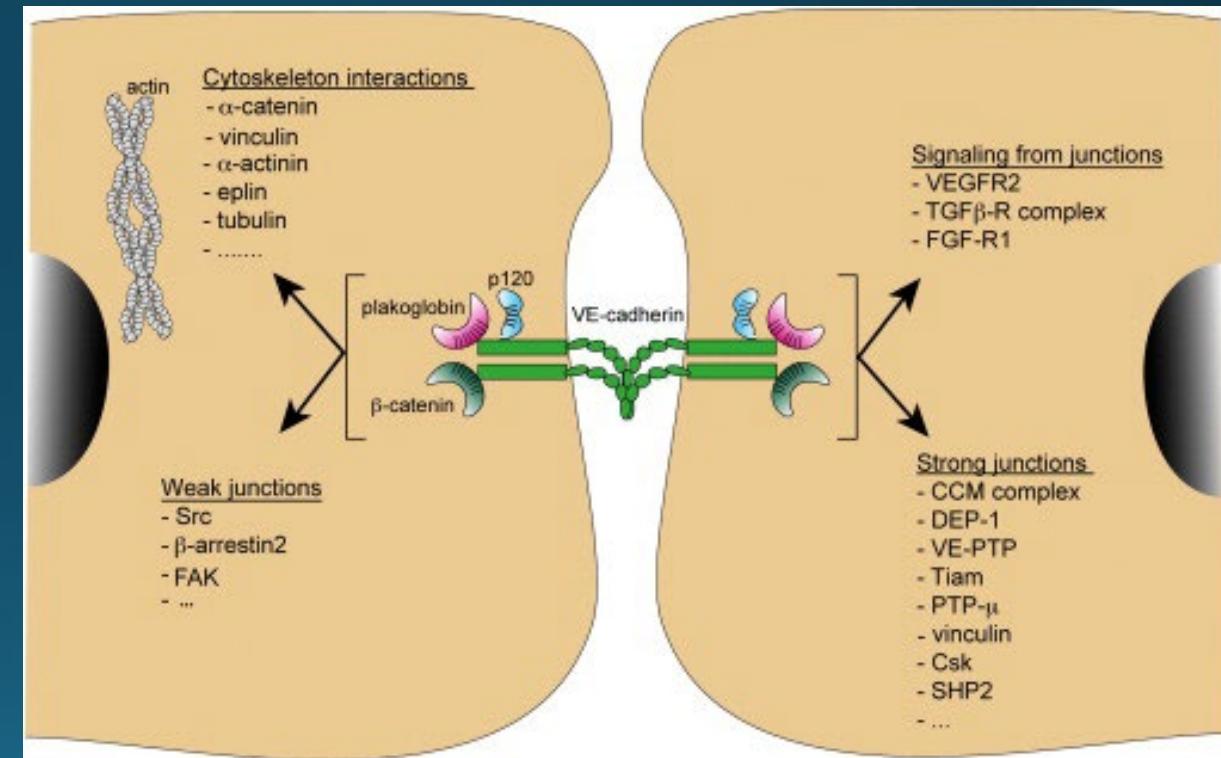
Pathophysiology

- Leptospiremia
 - Acute febrile illness
 - Lethargy
 - Hyporexia
 - Vomiting
 - Polydipsia / Polyuria
 - **May precede biochemical changes*



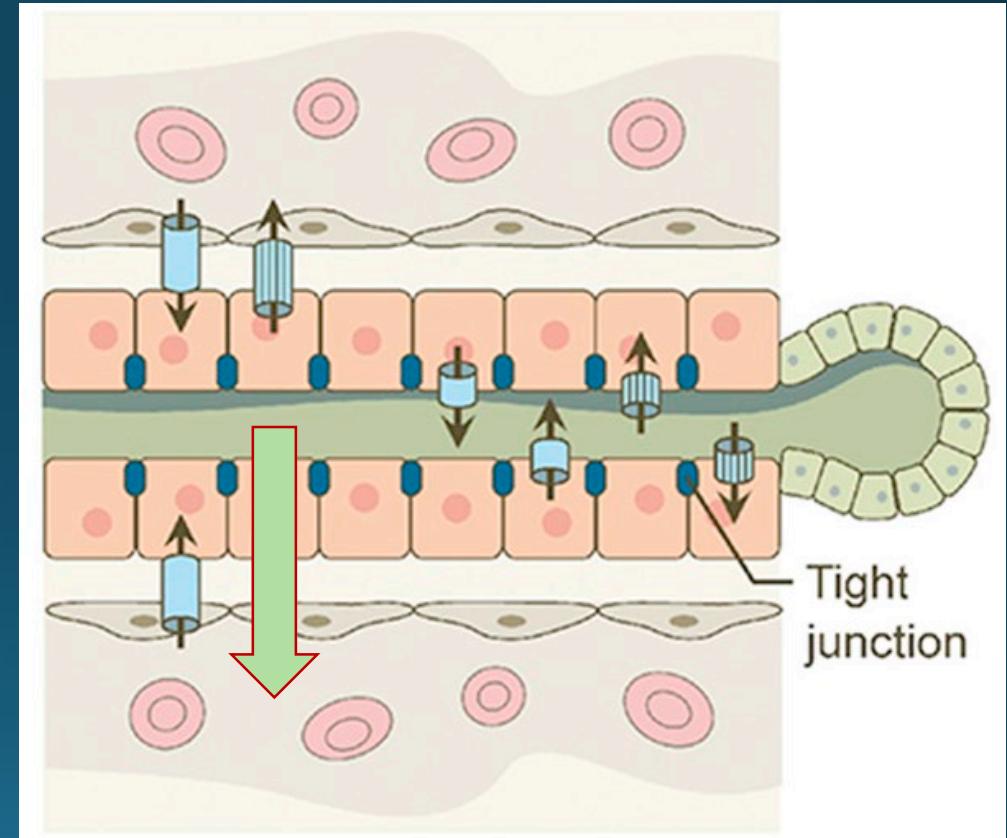
Pathophysiology

- **Vascular endothelial cadherin**
 - Acute tubulointerstitial nephritis
 - Myocarditis
 - Uveitis & Meningitis
 - Pancreatitis
 - Enteritis
 - Myositis
 - Vasculitis
 - Leptospiral pulmonary hemorrhage syndrome (LPHS)



Pathophysiology

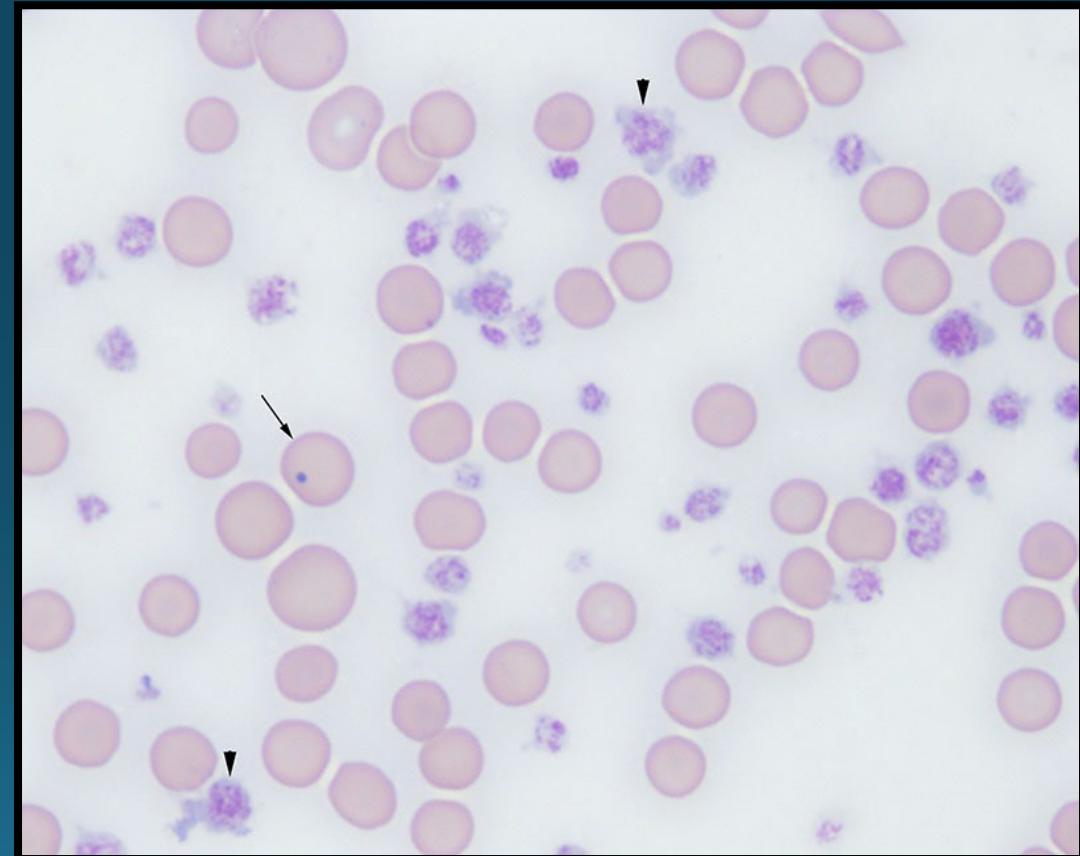
- **Hepatocyte intercellular junctions**
 - Bile leakage into circulation
 - Liver dysfunction
 - Cholestatic hepatopathy
 - *Ursodiol is contraindicated!*



<https://doi.org/10.1053/j.gastro.2018.06.048>

Pathophysiology

- **Coagulopathy**
 - Cytotoxic to platelets
 - Uremic thrombocytopenia & thrombocytopenia
- **Calcinosis cutis**
- **Abortion & Infertility**
- **Biofilm formation**
 - Immune privileged sites

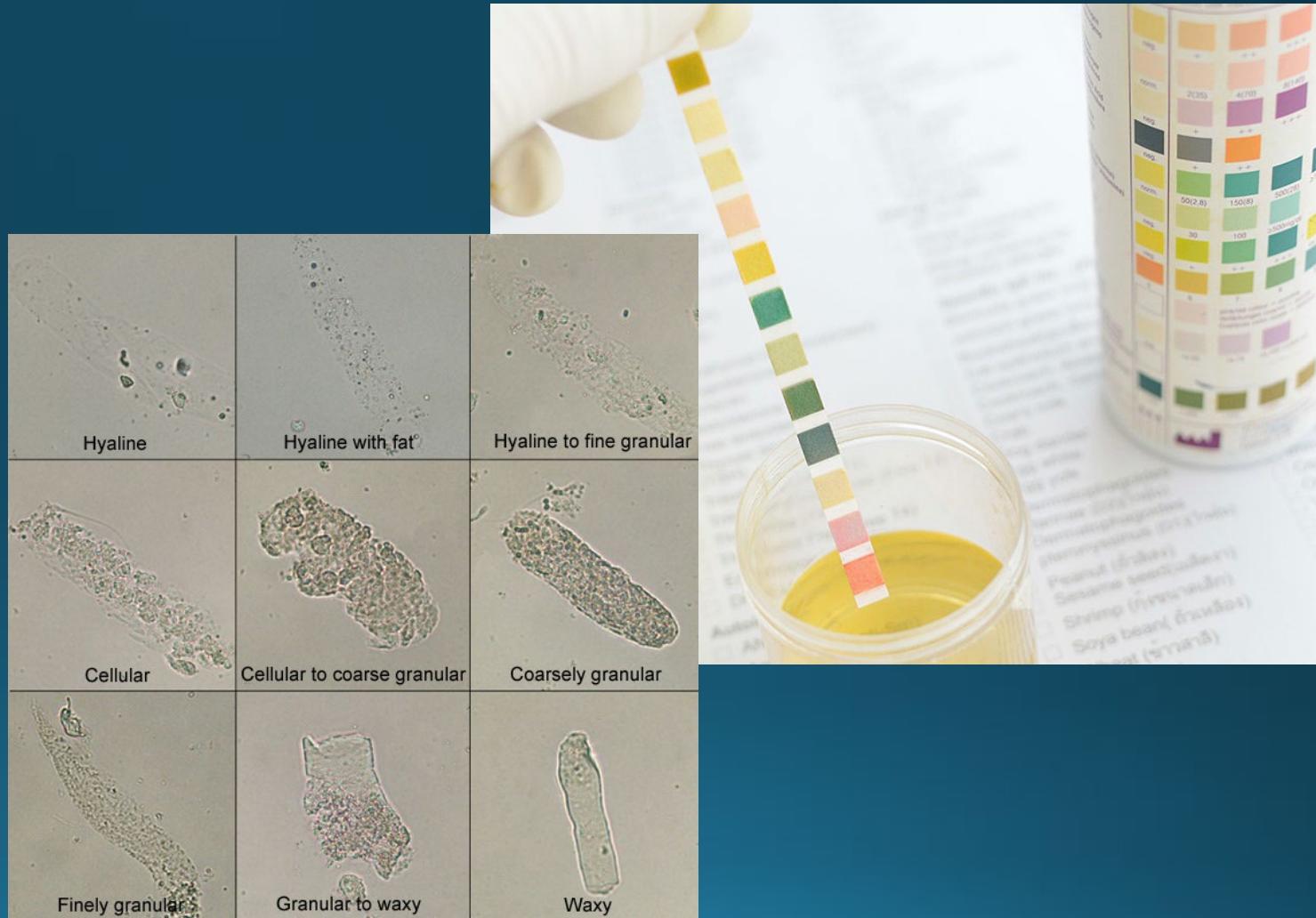


Pathophysiology: Clinicopathology

- CBC
 - Inflammatory leukogram
 - Thrombocytopenia
 - Non-regenerative anemia
- Electrolytes
 - Dec. Potassium
 - Non-oliguric
 - Inc. Potassium
 - Oliguric or anuric
- Chemistry
 - Azotemia
 - Hepatopathy
 - Cholestatic or mixed
 - Hypoalbuminemia
 - Inc. CK
 - Inc. Amylase / Lipase

Pathophysiology: Clinicopathology

- Urinalysis
 - USG 1.008-1.012
 - Glucosuria
 - Cylindruria
 - Proteinuria
 - Usually < 5
 - Up to 20!
 - Pyuria
 - Hematuria
 - Bilirubinuria



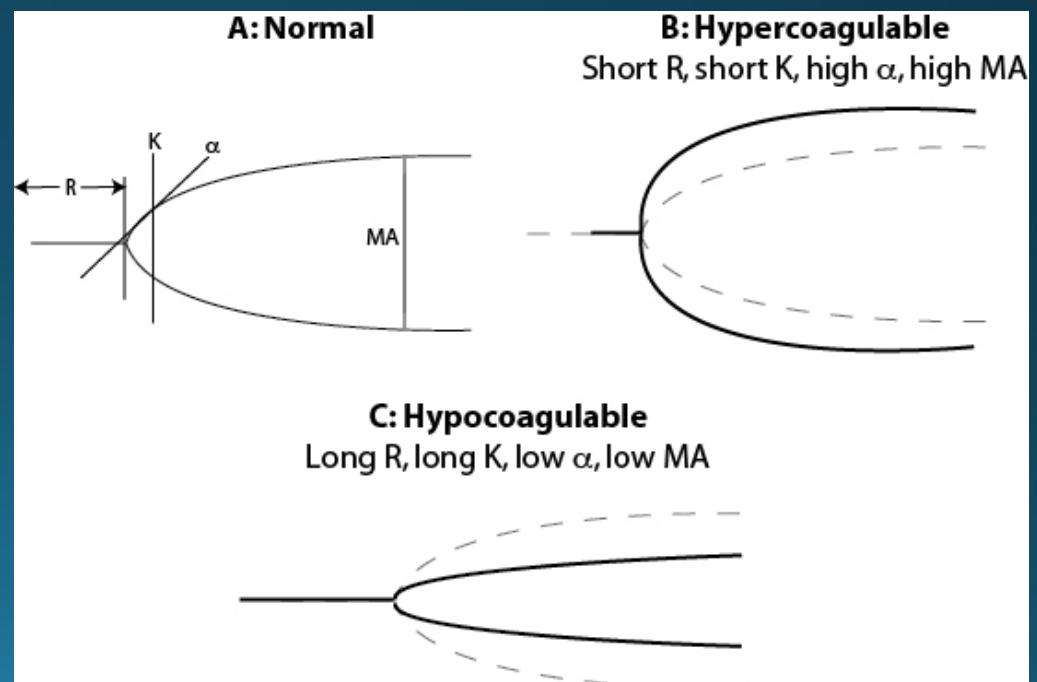
Pathophysiology: Clinicopathology

- Hemostasis

- Hypercoagulable (40%) > hypocoagulable (20%)
- Hyperfibrinogenemia > hypofibrinogenemia
- Prolonged aPTT > prolonged PT
- Dec. Antithrombin
- Inc. D-dimer

- Miscellaneous

- Inc. Troponin I
- Inc. C-reactive protein



Pathophysiology: Imaging



Pathophysiology: Imaging

- Leptospiral pulmonary hemorrhage syndrome
- Pleural effusion
 - Fluid overload
- Lobar alveolar pattern
 - Aspiration pneumonia



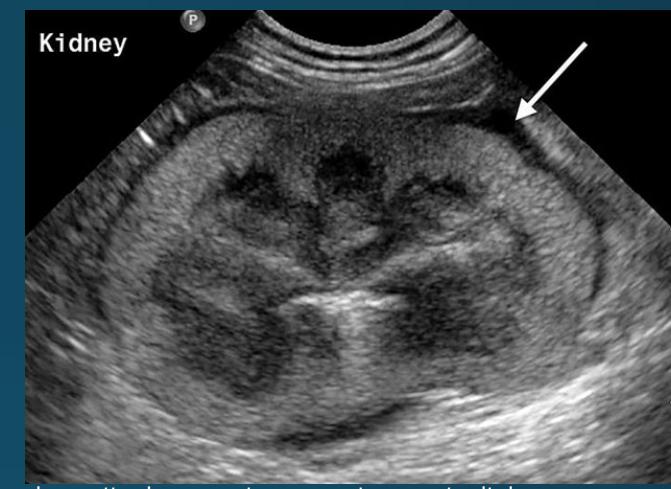
Pathophysiology: Imaging



DOI: 10.1111/vru.12069



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<https://todaysveterinarypractice.com/radiology-imaging/ultrasonography-peritoneal-retroperitoneal-spaces-abdominal-lymph-nodes/>



<https://www.soundwaveimaging.co.uk/services/abdominal-ultrasound/>



<https://www.cliniciansbrief.com/article/acute-pancreatitis-dogs>



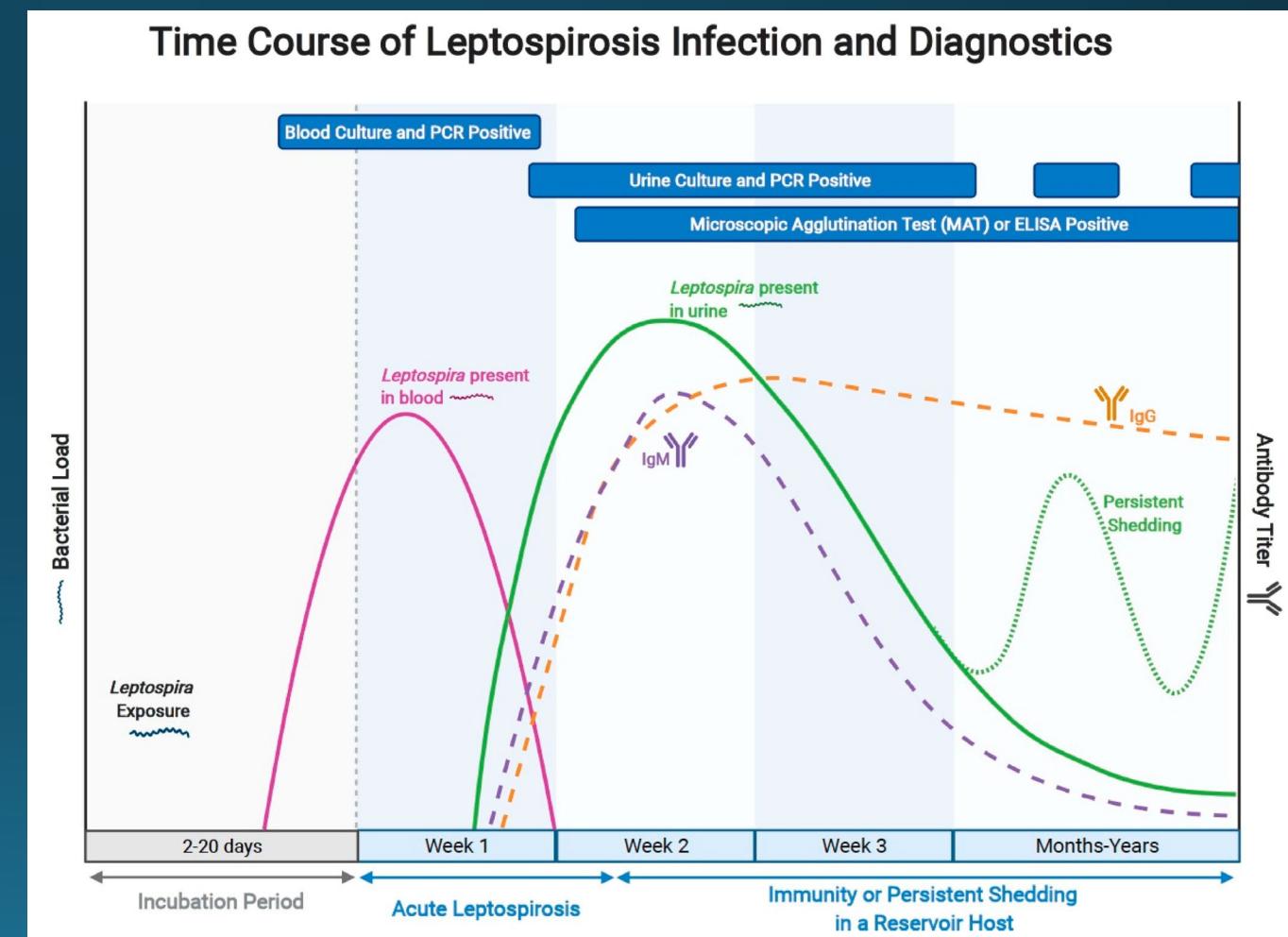
10.1111/j.1740-8261.1998.tb01617.x

Diagnosis

- Microscopic agglutination test (MAT)
- SNAP Lepto (IDEXX)
- Witness Lepto Rapid Test (Zoetis)
- Nucleic Acid Amplification Tests (NAAT)
- Darkfield Microscopy
- Culture
- All have limitations
- Use a combination of serologic assay + organism detection test

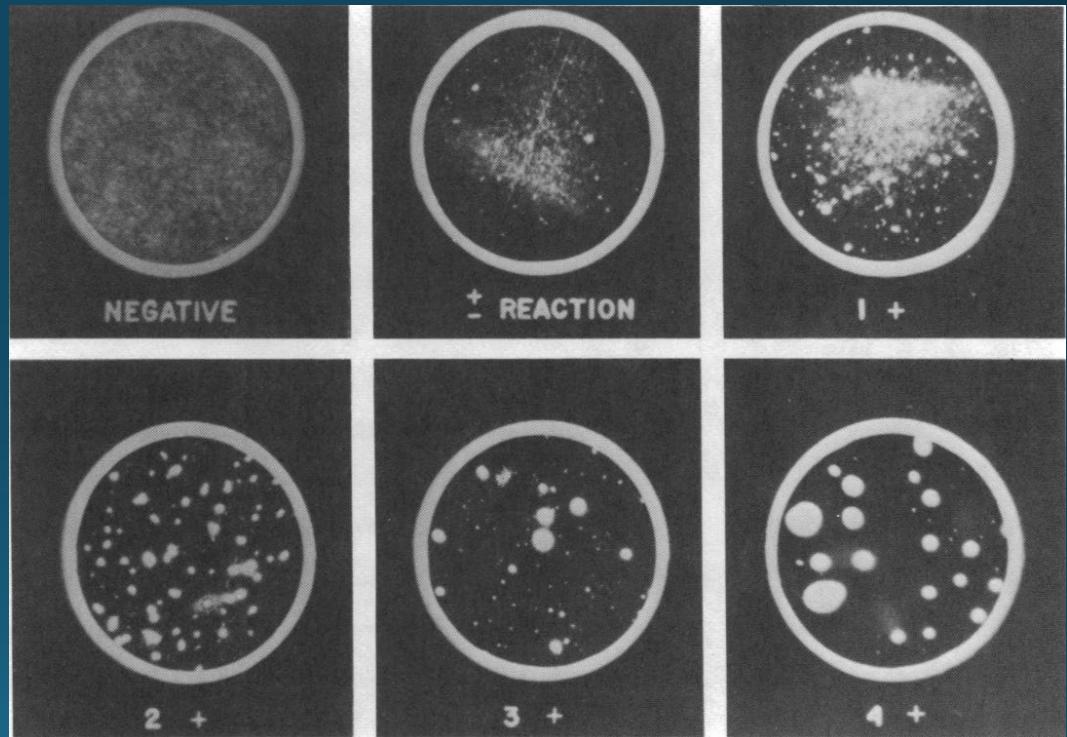
Diagnosis: Serology

- Titers after natural infection
 - Can persist for at least a year
- Titers after vaccination
 - Generally dec. by 4 months
 - Can persist longer with high titers ($\geq 1:1600$)



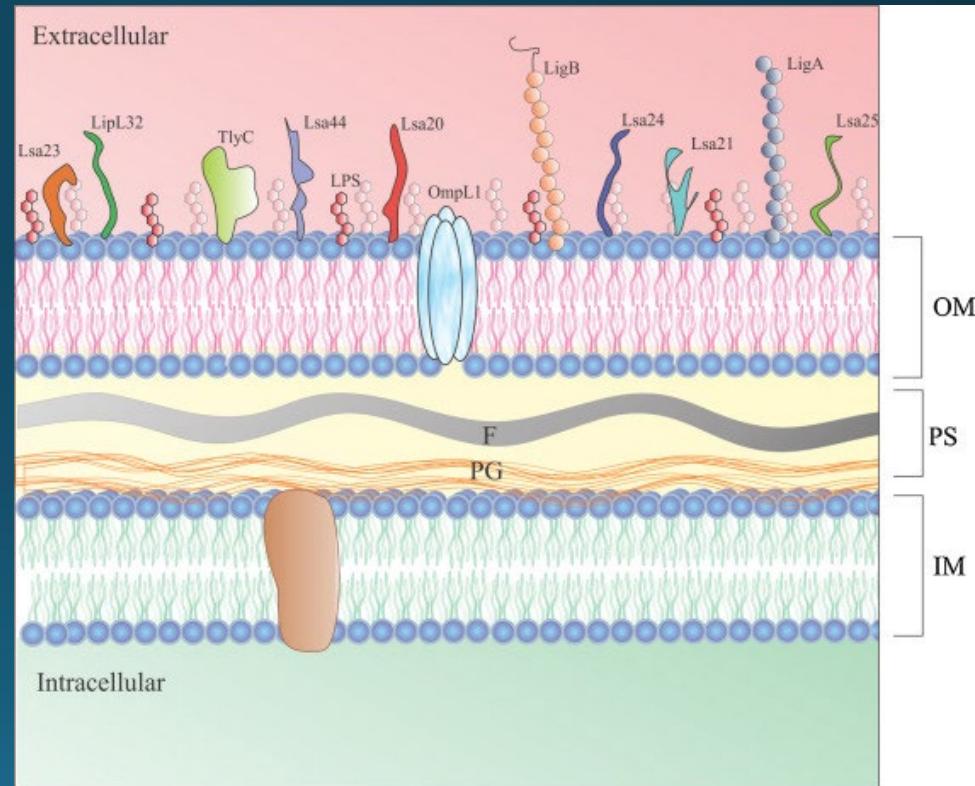
Diagnosis: Serology

- Microscopic agglutination test (MAT)
 - Acute & Convalescent, 7-14 days apart
 - False negative results
 - 6 to 8 serovars
 - Single MAT $> 1:800$ – 50% sensitivity
 - Incubation period & 1st week of illness
 - Antimicrobial treatment
 - False positive results
 - Recent vaccination
 - Recent subclinical exposure
 - Longer duration of illness than owner recognized**
 - Does not indicate infecting serovar



Diagnosis: Serology

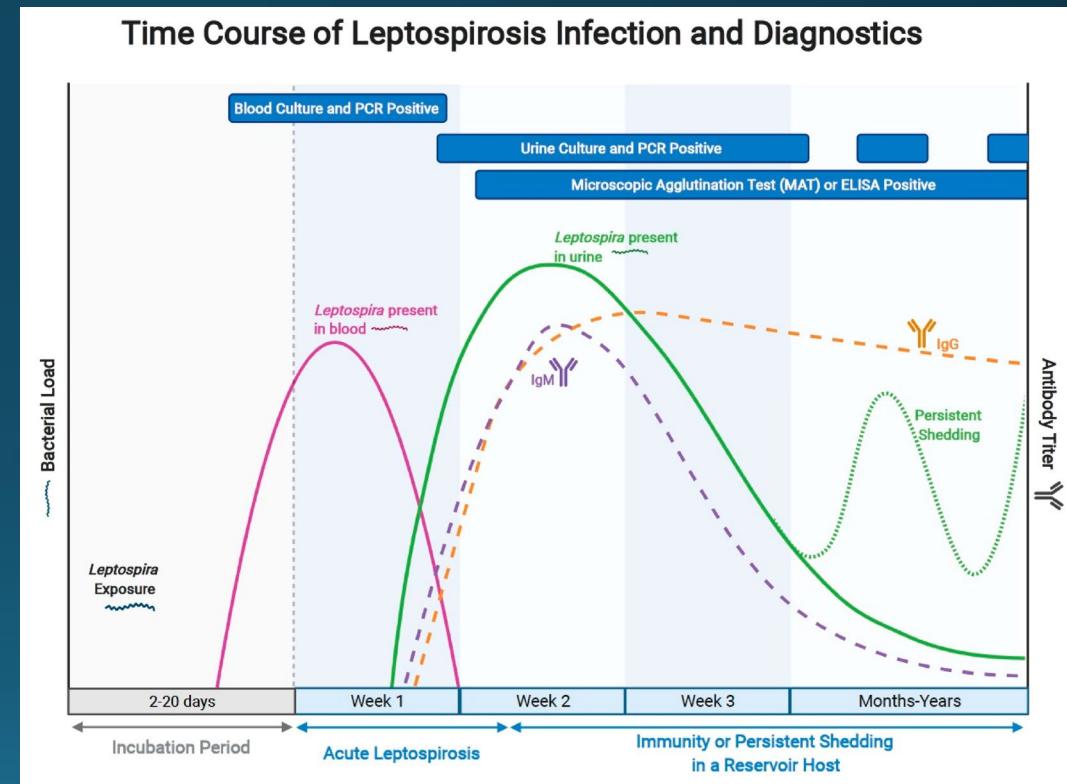
- SNAP Lepto (IDEXX)
 - LipL32 Antibodies
 - 96% specific
 - 83.2% agreement with MAT titers $\geq 1:800$
- Witness Lepto (Zoetis)
 - IgM to whole cell extract
 - *L. kirschneri* serovar Grippotyphosa
 - *L. interrogans* serovar Bratislava
 - 97% specific
 - 75% sensitivity



DOI: 10.1016/j.vetimm.2015.12.004

Diagnosis: Serology

- SNAP Lepto (IDEXX)
 - LipL32 Antibodies
 - 96% specific
 - 83.2% agreement with MAT titers $\geq 1:800$
- Witness Lepto (Zoetis)
 - IgM to whole cell extract
 - *L. kirschneri* serovar Grippotyphosa
 - *L. interrogans* serovar Bratislava
 - 97% specific
 - 75% sensitivity



DOI: 10.3390/pathogens11040395

Diagnosis: Serology

Location	Point-of-care test	Sensitivity	Specificity	Reference
Northeastern US	IDEXX SNAP Lepto	15/22 (68%)	111/131 (85%)	107
Germany	Zoetis WITNESS	28/37 (76%)	59/60 (98.3%)	104
Italy	Zoetis WITNESS	30/42 (71%)	36/36 (100%)	105
	IDEXX SNAP Lepto	33/42 (79%)	26/36 (72%)	
Switzerland	Zoetis WITNESS	31/41 (76%)	28/28 (100%)	106

Diagnosis: Organism Detection

- Nucleic Acid Amplification Tests (NAAT)
 - Prior to antibiotic
 - Blood & urine
 - False negatives
 - Some assays do not detect P2 species
 - Intermittent urinary shedding
 - Presence of urinary inhibitors of NAA
 - Heparin (green-top)
 - Storage
 - “False positives”
 - *DNA of pathogenic leptospires can be found in urine of up to 20% of apparently healthy dogs and cats*
- Darkfield Microscopy
- Culture

Diagnosis: Organism Detection

- Nucleic Acid Amplification Tests (NAAT)
- Darkfield Microscopy
 - Low sensitivity – not recommended for routine diagnosis
- Culture
 - Low sensitivity – not recommended for routine diagnosis
 - Useful for determining infective strains during outbreaks
 - Required for vaccine selection

Case Definitions

- Probable case
 - Meets clinical criteria
 - ≥ 1 supportive laboratory criteria
- Confirmed case
 - Meets clinical criteria
 - ≥ 1 confirmatory laboratory criteria

3.1.1 | CLINICAL CRITERIA

1. Onset of systemic illness (nonspecific fever, lethargy, polyuria, polydipsia, anorexia, or some combination of these signs) within the past 2 weeks, with or without other clinical signs suggestive of leptospirosis:
 - a. Gastrointestinal (vomiting, diarrhea, abdominal pain)
 - b. Pulmonary (tachypnea, cough, hemoptysis)
 - c. Ocular (uveitis, conjunctivitis, scleral injection, punctate retinal hemorrhages)
 - d. Clinical suspicion for AKI (oliguria/anuria)
 - e. Icterus
 - f. Hemorrhage (ecchymoses, petechiae, epistaxis, hematuria, melena, hematemesis)
2. Two or more of the following clinicopathologic abnormalities:
 - a. Neutrophilic leukocytosis, with or without a left shift
 - b. Thrombocytopenia
 - c. Biochemical evidence of AKI (eg, isosthenuria together with increased serum creatinine or symmetric dimethyl arginine [SDMA] concentrations or both)
 - d. Biochemical evidence of cholestatic hepatopathy
 - e. Biochemical evidence of pancreatitis (increased serum pancreatic lipase or DDGR-lipase activity)
 - f. Increased CK activity
 - g. Glucosuria despite normoglycemia
 - h. Active urine sediment (pyuria or granular casts)
 - i. Radiographic findings consistent with pulmonary hemorrhage syndrome
 - j. Abdominal ultrasonographic findings consistent with leptospirosis (findings supportive of pancreatitis, hyperechoic renal cortices, perirenal fluid)
 - k. ECG-documented cardiac arrhythmias or increased serum troponin concentration

Case Definitions

- Probable case
 - Meets clinical criteria
 - ≥ 1 supportive laboratory criteria
- Confirmed case
 - Meets clinical criteria
 - ≥ 1 confirmatory laboratory criteria

3.1.2 | SPECIFIC LABORATORY CRITERIA

Diagnostic testing should be performed in dogs that meet clinical criteria. Although a history of potential exposure (predation, exposure to other animal species or water sources) should increase suspicion for leptospirosis, all dogs should be considered at risk, regardless of signalment, geographic region, and lifestyle.

Supportive:

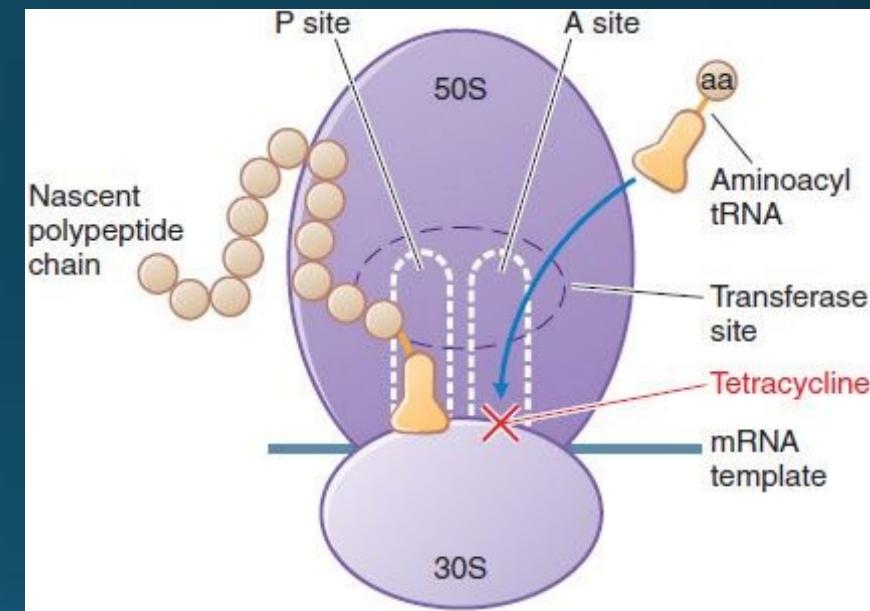
- a. *Leptospira* MAT titer ≥ 800 in ≥ 1 serum specimens
- b. Detection of IgM antibodies against *Leptospira* in an acute phase serum specimen
- c. Detection of pathogenic leptospires in urine using a NAAT
- d. Visualization of spirochetes in a blood or urine specimen using darkfield microscopy by a *Leptospira* reference laboratory

Confirmatory:

- a. Fourfold or higher increase in *Leptospira* agglutination titer at a single laboratory between acute- and convalescent-phase serum specimens
- b. Detection of pathogenic leptospires in blood using a NAAT
- c. Isolation of *Leptospira* from a clinical specimen by a *Leptospira* reference laboratory

Treatment: Antibiotics

- Doxycycline 5mg/kg PO q12h x 2 weeks
 - DO NOT COMBINE WITH DAIRY or ANTACIDS containing Ca++, Mg++, Al+++
- Ampicillin 20-30 mg/kg IV q6-8h
 - Patients with gastrointestinal signs
 - Q12h if AKI IRIS \geq grade 4 ($\text{Cr} > 5.0 \text{ mg/dL}$)



ISBN-13: 978-1264258079

Treatment: Supportive Care

- Correct dehydration and prevent hypovolemia
- Correct hypotension
- Antihypertensives
 - Amlodipine 0.25-0.75mg/kg/day PO
- Correct acid-base and electrolyte derangements
- Antiemetics
- Nutritional support
- Oxygen supplementation
- Mechanical ventilation
- Hemostasis
- Diuretics?
- Hepatoprotectants?



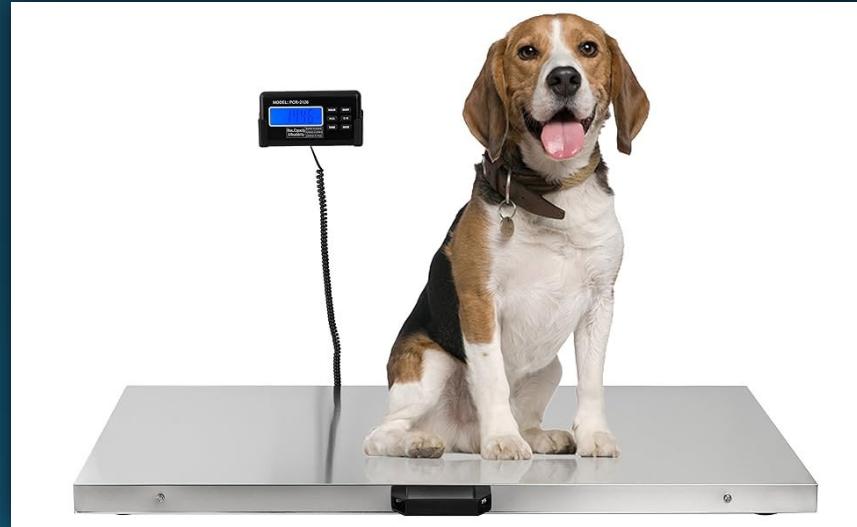
Treatment: Dialysis

- Indications
 - Hyperkalemia
 - Severe azotemia
 - IRIS AKI \geq Grade 4 ($\text{Cr} > 5.0 \text{ mg/dL}$)
 - Fluid imbalance
 - Metabolic acidosis
- 1 to 2 weeks
- Early intervention recommended
- >80% success



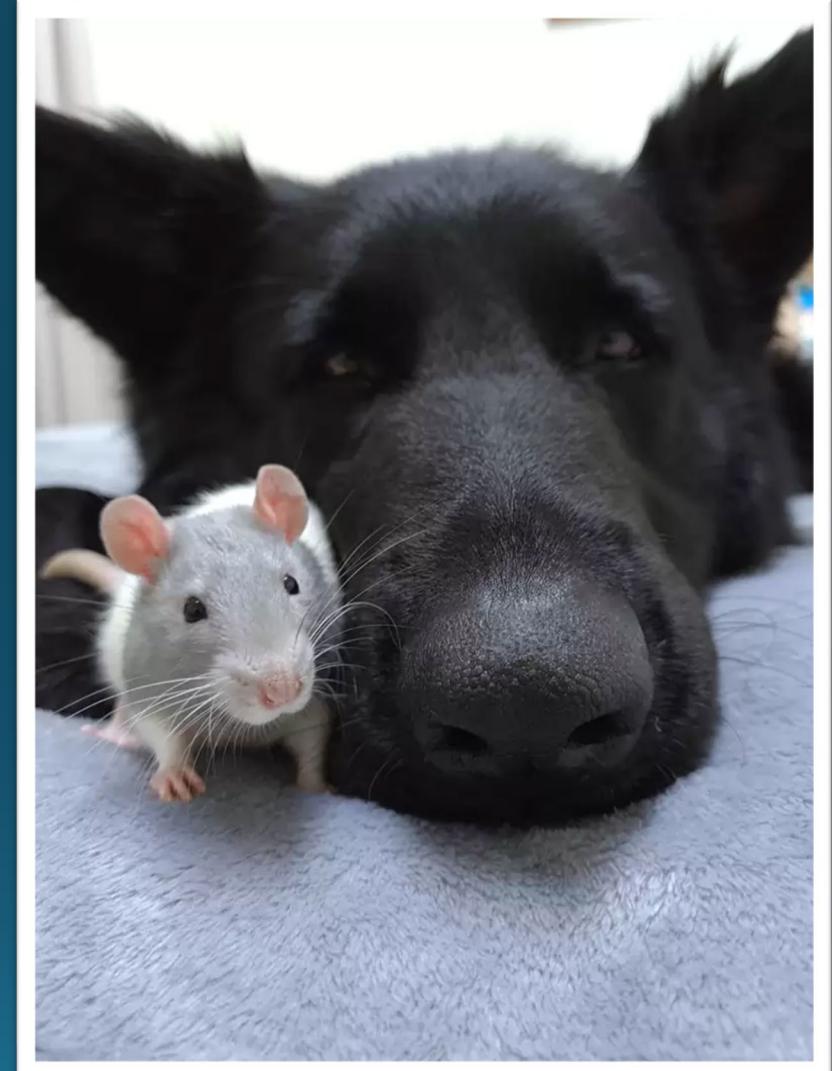
Treatment: Monitoring

- Chemistry q24h
- PCV/TS q24h
- CBC q48h
- Urine output Q4-6h
 - Indwelling catheter with closed collection system
- Body Weight Q4-6h
 - Q3h for anuric or severely polyuric dogs
- ***Taper off IV fluids and discharge once azotemia resolves or stabilizes and the patient can maintain hydration and vascular volume***



Treatment: Monitoring

- 1 week recheck
 - CBC
 - Chemistry
 - USG
 - +/- convalescent titers



Prognosis

- Resolution of azotemia within 10 to 14 days
- Renal compensatory hypertrophy over weeks to months
- Residual damage may remain long-term
- Total bilirubin decreases slower than ALT or ALP
- PLT normalizes within one week of antibiotic treatment
- C-reactive protein decreases within 4 to 10 days
 - Serial monitoring?



Negative Prognostic Indicators

- Hyperbilirubinemia
 - T_{bili} ≥ 0.6 is associated with 16.4x increased risk of death or euthanasia
- Hypercoagulability
- DIC
- Pancreatitis
- Anuria
- Higher AKI IRIS Grade
- LPHS
 - Associated with up to 70% mortality



Prevention: Vaccination

- Nobivac – Lepto-4 (1 mL)
- Nobivac – Lepto-4 Edge (0.5 mL)
- Nobivac – DAPPv+L4 (1 mL)
- Nobivac – DAPPv+L4 Edge (1 mL)
- Vanguard (Zoetis) – L4
- Vanguard (Zoetis) – DAPP/L4

- Vanguard (Zoetis) – DAPP/L4+CV
- Rocombitek (Boehringer Ingelheim) - 4 Lepto
- Trucan (Elanco) – Ultra L4
- Trucan (Elanco) – Ultra DAP+L4
- Trucan (Elanco) – Ultra DAP+CL4



Prevention: Vaccination

- Bacterins = killed or attenuated bacteria
 - 4-way: Icterohaemorrhagiae, Canicola, Grippotyphosa, Pomona
 - 2-way: Icterohaemorrhagiae, Canicola
 - 1-way: Icterohaemorrhagiae
- Prevent disease
- Decrease shedding
- Protective for >12 months



Prevention: Vaccination

- Similar adverse rates as distemper-parvovirus and rabies vaccines
- *Recommended for all dogs regardless of age, geography, or lifestyle*
- *Should be required for dogs in boarding or daycare facilities*
- *Recommended as soon as possible after recovery from leptospirosis*
- *Not approved for cats*



Prevention

- All dogs with AKIs are suspect
- Isolation
 - Floor-level cages
 - Away from high traffic areas
- Decrease access to sources of infection
 - Walk patients frequently in restricted and inhabitable areas
- Antimicrobial treatment for > 48 hours
- Disposal of medical waste in biohazard bags
 - Disposable bedding
 - Closed collection system - 1:1 dilution with 10% bleach



Prevention: Standard Hygiene

- Hand hygiene
- Personal protective equipment
- Avoid pressure washing or aerosols
- Laundry
 - Wear gloves and protective outerwear
 - Standard laundry detergent + highest temperature drying
 - Separate dirty and clean bins
- EPA-registered disinfectants
 - Alcohols, alkalis, aldehydes, halogens (chlorine, iodine), oxidizing agents, phenols, +/- quaternary ammonium compounds



Disinfectant Category	Alcohols	Alkalis	Aldehydes	Oxidizing Agents			Phenols	Quaternary Ammonium Compounds
				Halogens: Chlorine	Halogens: Iodine	Peroxygen Compounds		
Common Active Ingredients	•ethanol •isopropanol	•calcium hydroxide •sodium carbonate •calcium oxide	•formaldehyde •glutaraldehyde •ortho-phthalaldehyde	•sodium hypochlorite (bleach) •calcium hypochlorite •chlorine dioxide	•providone-iodine	•hydrogen peroxide/ accelerated HP •peracetic acid •potassium peroxyomonosulfate	•ortho-phenylphenol •orthobenzylpara-chlorophenol	•benzalkonium chloride •alkyldimethyl ammonium chloride
Sample Trade Names*			Synergize®	Clorox®, Wysiwash®		Rescue®, Oxy-Sept 333®, Virkon-S®	One-Stroke Environ®, Pheno-Tek II®, Tek-Trol®, Lysol®	Roccal-D®, DiQuat®, D-256®
Mechanism of Action	Precipitates proteins; denatures lipids	Alters pH through hydroxyl ions; fat saponification	Denatures proteins; alkylates nucleic acids	Denatures proteins	Denatures proteins	Denature proteins and lipids	Denatures proteins; disrupts cell wall	Denatures proteins; binds phospholipids of cell membrane
Characteristics	• Fast acting • Rapid evaporation • Leaves no residue • Can swell or harden rubber and plastics	• Slow acting • Affected by pH • Best at high temps • Corrosive to metals • Severe skin burns; mucous membrane irritation • Environmental hazard	• Slow acting • Affected by pH and temperature • Irritation of skin/mucous membrane • Only use in well ventilated areas • Pungent odor • Noncorrosive	• Fast acting • Affected by pH • Frequent application • Inactivated by UV radiation • Corrodes metals, rubber, fabrics, • Mucous membrane irritation	• Stable in storage • Affected by pH • Requires frequent application • Corrosive • Stains clothes and treated surfaces	• Fast acting • May damage some metals (e.g., lead, copper, brass, zinc) • Powdered form may cause mucous membrane irritation • Low toxicity at lower concentrations • Environmentally friendly	• Can leave residual film on surfaces • Can damage rubber, plastic; non-corrosive • Stable in storage • Irritation to skin and eyes	• Stable in storage • Best at neutral or alkaline pH • Effective at high temps • High concentrations corrosive to metals • Irritation to skin, eyes, and respiratory tract
Precautions	Flammable	Very caustic	Carcinogenic	Toxic gas released if mixed with strong acids or ammonia			May be toxic to animals, especially cats and pigs	
Bactericidal	+	+	+	+	+	+	+	+
Virucidal	± ^a	+	±	+	+	+	+	+ Enveloped
Fungicidal	+	+	+	+	+	±	+	+
Tuberculocidal	+	±	+	+	+	±	+	—
Sporicidal	—	+	+	+	±	+	—	+
Factors Affecting Effectiveness	Inactivated by organic matter	Variable	Inactivated by organic matter, hard water, soaps and detergents	Rapidly inactivated by organic matter	Rapidly inactivated by organic matter	Effective in presence of organic matter, hard water, soaps, and detergents	Effective in presence of organic matter, hard water, soaps, and detergents	Inactivated by organic matter, hard water, soaps and anionic detergents

Prevention: Client Education

- Leptospiruria occurs ~7-10 d. after illness onset
- 48 hr of antibiotics likely prevents leptospiruria
- Owners should contact their physician
- Prophylactic treatment of other dogs in home



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