Chagas Disease and Veterinary Medicine

Tracking a Neglected Disease

Presenters: Dr. Roy Madigan and Dr. Shannon McBride

September 29th, 2023

Disclosure of Relevant Financial Relationships

Chagas Disease in the United States
ECHO: Extension for Community Health Outcomes

September 29th, 2023 Virtual Learning Event

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Roy Madigan, DVM, Shannon McBride, DVM,

and Planning Committee Members

Agenda

- Welcome
- Introductions and Announcements
- Didactic Presentation and Treatment
  - Dr. Roy Madigan
- Case Presentation
  - Dr. Shannon McBride
- Q&A
- Closing Remarks

ROY MADIGAN, DVM

DIRECTOR OF THE ANIMAL HOSPITAL OF SMITHSON VALLEY
DOCTOR OF VETERINARY MEDICINE
TEXAS A&M UNIVERSITY

Dr. Madigan is a 2001 graduate of the Texas A&M University College of Veterinary Medicine. He has been serving as director of the Animal Hospital of Smithson Valley in the Spring Branch/Bulverde community for over 15 years now; focusing on small animal companion animals. It was there that he fostered a passion for treating Chagas disease, and made it his mission to increase awareness of it to the public.

Currently, he is working internationally on a canine and human treatment for this disease, and founded a non-profit pharmaceutical company devoted to serving impoverished communities through the development of treatments for neglected diseases.

SHANNON MCBRIDE, DVM

DOCTOR OF VETERINARY MEDICINE
PHD STUDENT IN PUBLIC HEALTH
SAN DIEGO STATE UNIVERSITY

Dr. McBride is a veterinarian with a passion for zoonotic and vector-borne diseases. She graduated from Washington State University College of Veterinary Medicine in 2015, where she gained an interest in public and global health.

After graduating from vet school, Dr. McBride gained practice experience in equine sports medicine and small animal relief work. She is currently finishing her Master of Public Health degree at San Diego State University and starting her PhD in global health in the joint doctoral program at SDSU and UCSD. In 2021, she began working with Dr. Paula Granados on Chagas disease research.

Dr. McBride's interests lie broadly with zoonotic and vector-borne diseases, but she is particularly interested in Chagas disease. She is committed to using her research and expertise to improve the prevention, surveillance, diagnosis, and treatment of zoonotic and vector-borne diseases.

CME AND DVM CREDITS AVAILABLE

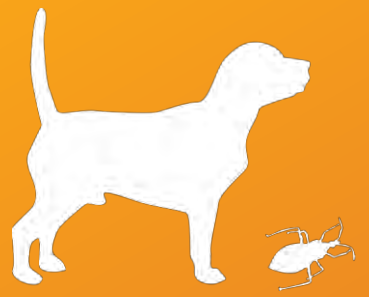
Please remember to fill out the evaluation after this session if you are interested in receiving one hour of CME or DVM continuing education credits.

https://qfreeaccountssjc1.az1.qualtrics.com/jfe/form/SV_2mHG1rQJtrgc19A

Announcements

- This session will be recorded and be made available online at the UT Health San Antonio ECHO website
- Evaluations will be sent out via email after this session
- CME certificates will be issued within 3 weeks following this session
- If you have any questions, please reach out to **chagasus@gmail.com**

This work is supported by the Cooperative Agreement Number, 6 NU2GGH002323-01-01, funded by the Centers for Disease Control and Prevention. The contents of this webinar are solely the responsibility of the presenters and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.



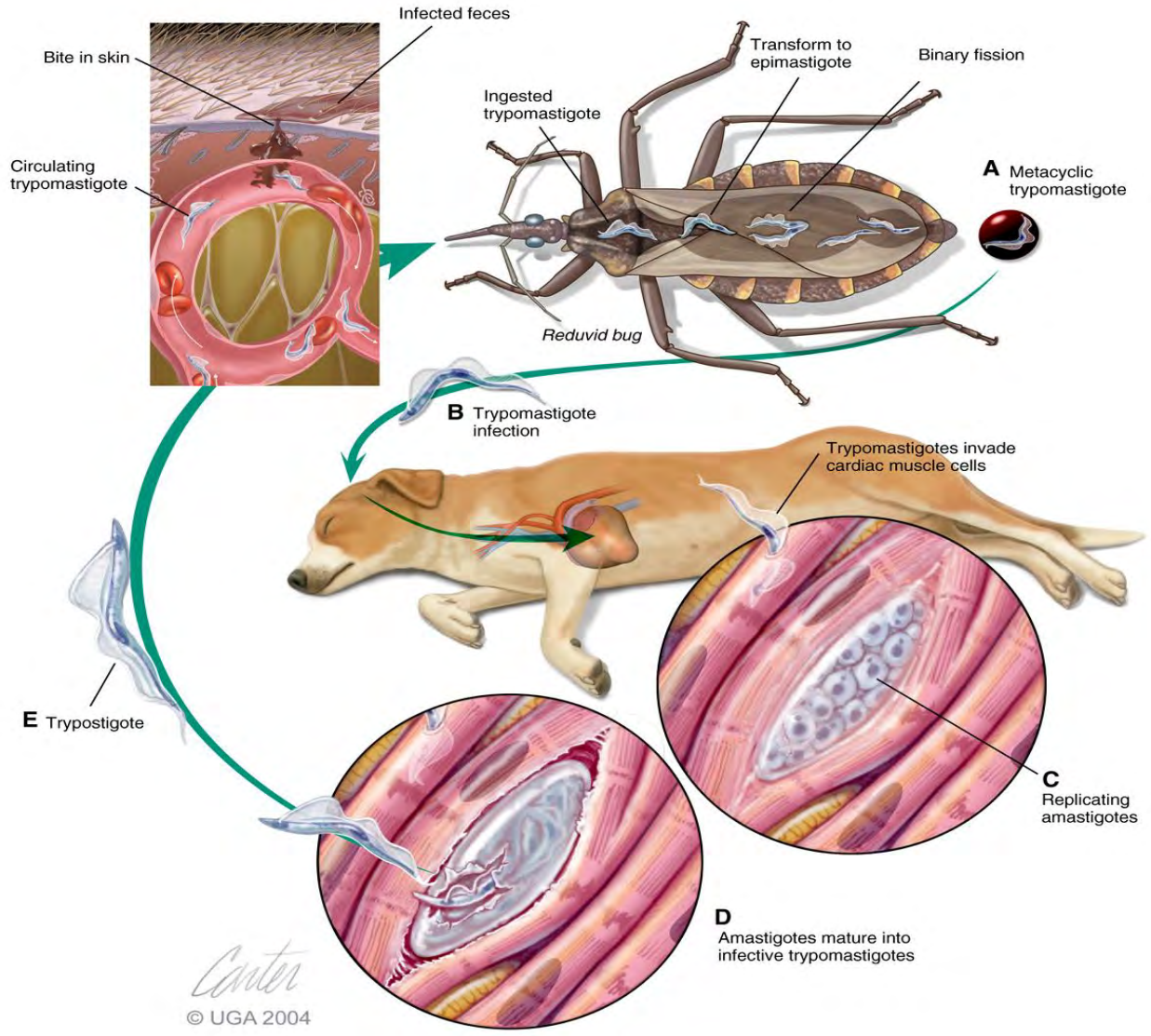
Chagas for Veterinarians

Boot Camp 2023

Vida Pharmacal

Chagas Disease

American Trypanosomiasis

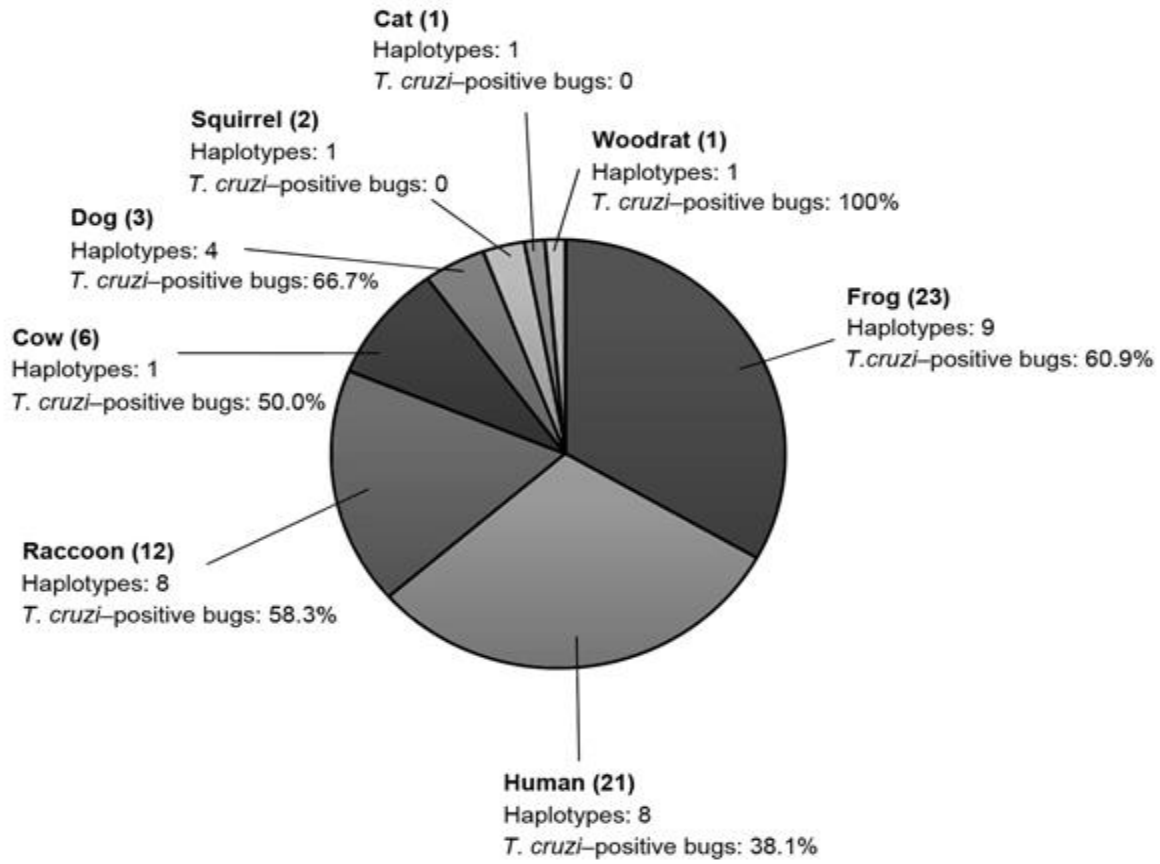


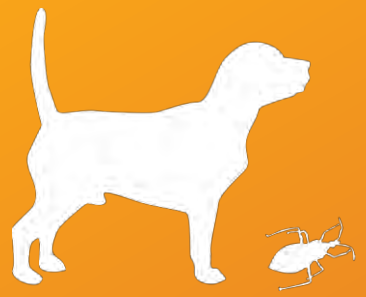
Chagas Disease

Blood Meal Analysis

- Kissing Bug
- 7 species found in Texas
- Most active in Warm Summer months
- >60% infected with *T. Cruzi*
- Animal Reservoirs Opossum, raccoon, rat

Triatoma sanguisuga Blood Meals Louisiana, USA
Waleckx et al 2014





Canine Prevalence

Epidemiology

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Chagas Disease

Prevalence

Louisiana HW 7.1% positive

22% Companion dogs

Tennessee HW 2.7% positive

6.4% Companion dogs

Texas (~630,000 infected) HW 3.3% positive

18% Shelter dogs

13.6% Companion dogs San Antonio region

8% U.S. Military Working dogs

Oklahoma HW 2% positive

3.6% Companion dogs

California HW 0.42% positive

15% Shelter dogs San Francisco

60% Companion dogs Marin county (SF)

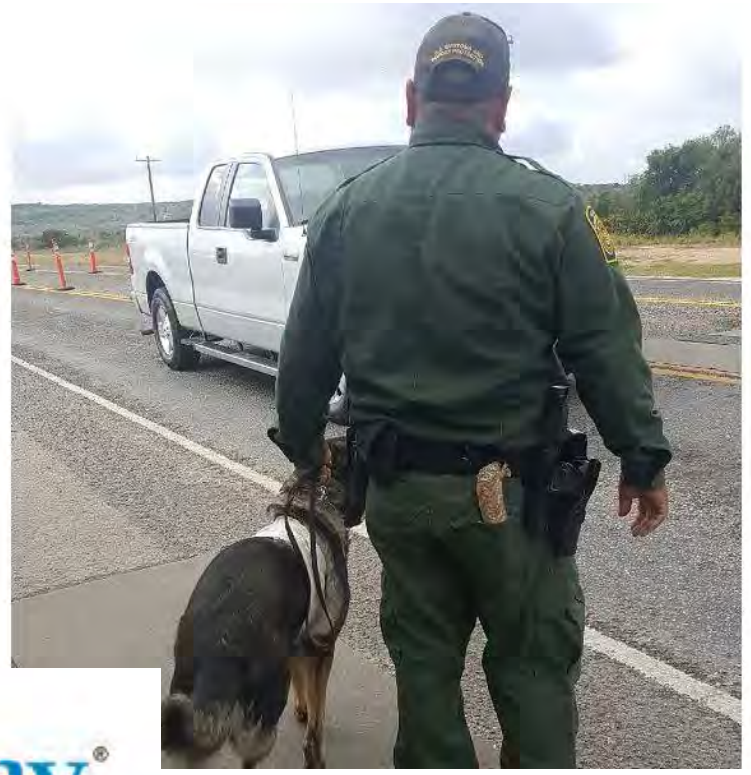
Chagas Disease

Prevalence

Tropical Disease Linked to Heart Trouble Turning Up in Border Security Dogs

(November 1, 2018)

- 1660 U.S. working dogs sampled in 43 states
- 121 Chagas positive (7.3%)
- "We were not expecting infection in dogs that spend most of their time working along the border with Canada or in airports in Nebraska."



HealthDay
News for Healthier Living

Chagas Disease

Texas Prevalence

Shelter Dogs Prevalence

- Heartworm disease

  16%

- Ehrlichia spp

  3.6%

- Anaplasma spp

  6.9%

- Borrelia burgdorferi

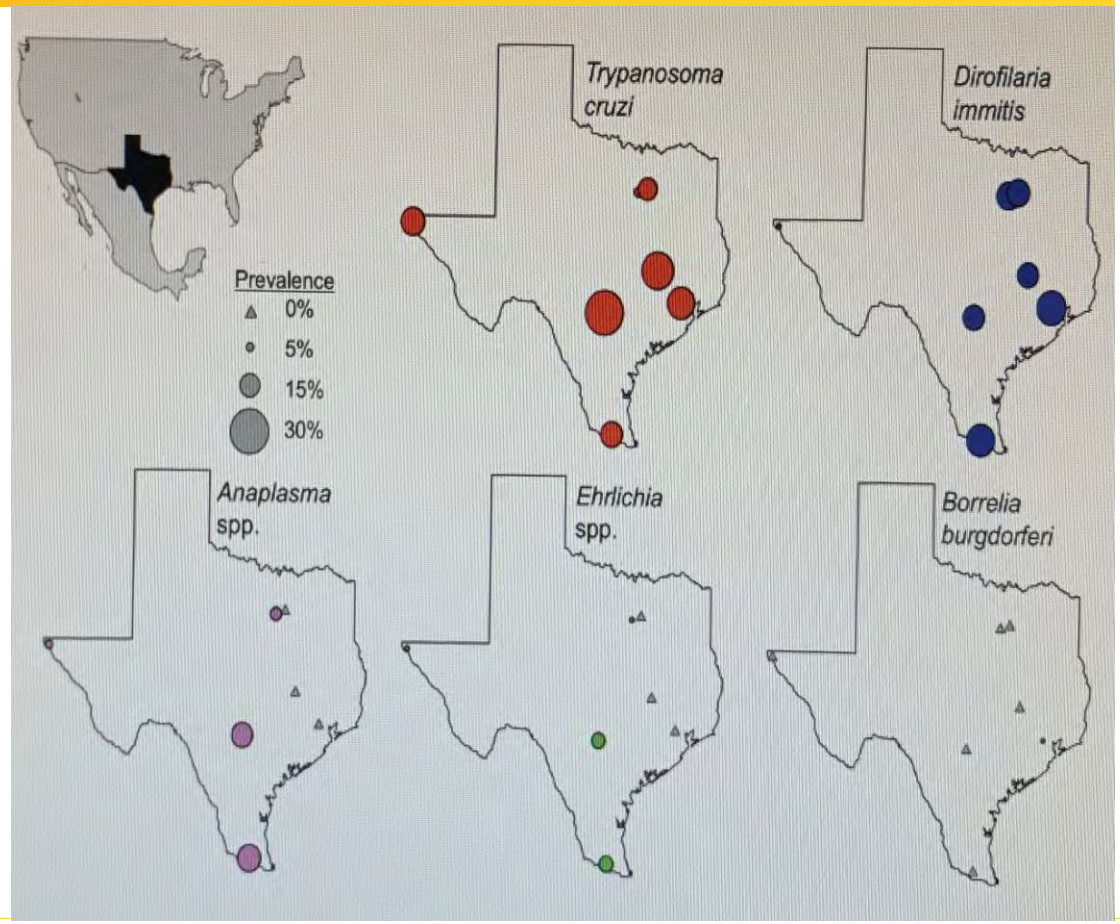
  0.2%

- Chagas disease

  18% (~380,000 positive)

By the way…

20% of **HW +** dogs also **Chagas +**



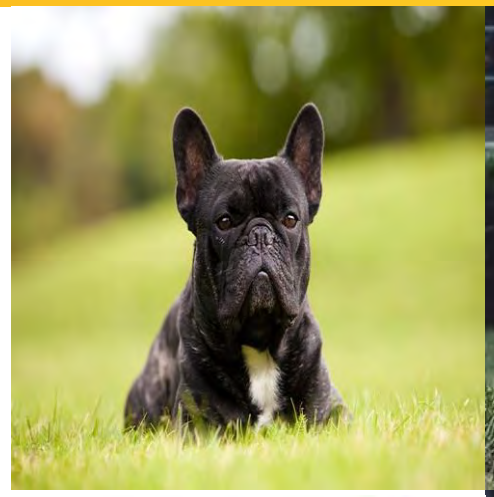
Chagas Disease

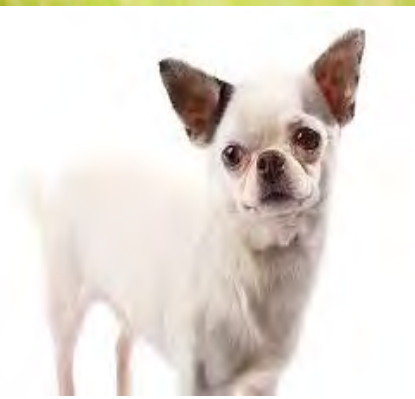
Prevalence

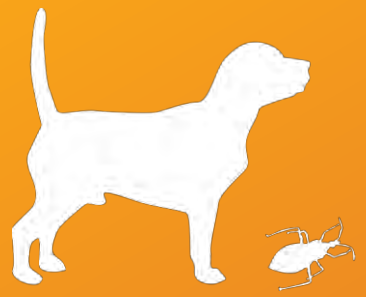
Breed Distribution

1. **English/French Bulldog** (54%)
2. **German Shepherd** (30%)
3. **Chihuahua** (29%)
   - Overall Prevalence 16.8%
     - Similar to shelter dog population 18%
   - Client owned dogs
   - Reason for testing?
     - Arrhythmia
     - Packmate infected

Meyers et al 2021 JVIM







Pathogenesis

Behind the Scenes

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Chagas Disease

Pathogenesis

Inflammation

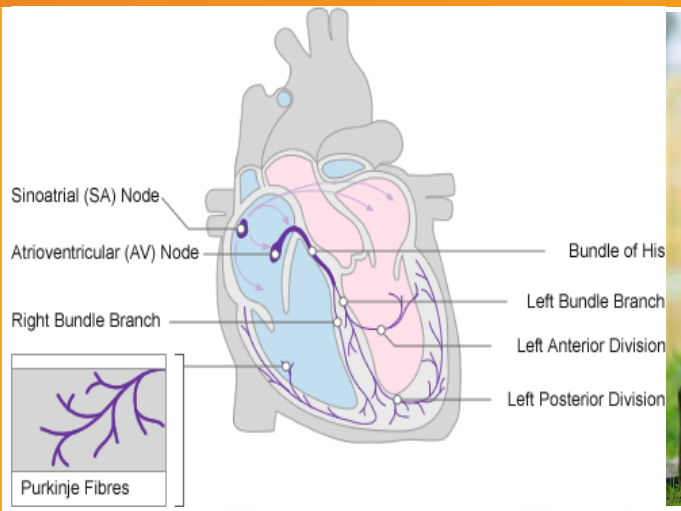
- Host immunity/genetics
- Strain dependent
- Route dependent

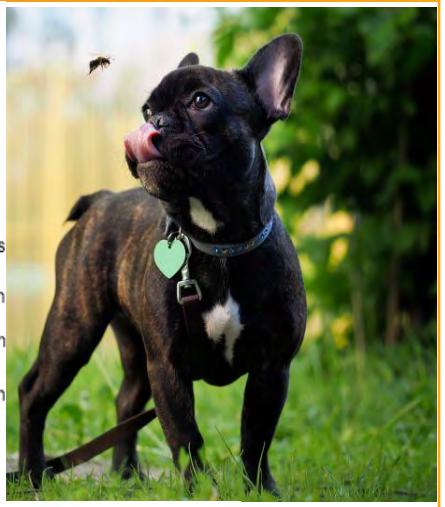
Neurogenic disturbances

- Dysautonomia
  - Parasympathetic denervation precedes cardiovascular signs
  - Primary cause of arrhythmias

Microvascular derangements

- Endothelial cell damage
- Microthrombi
- Ischemia



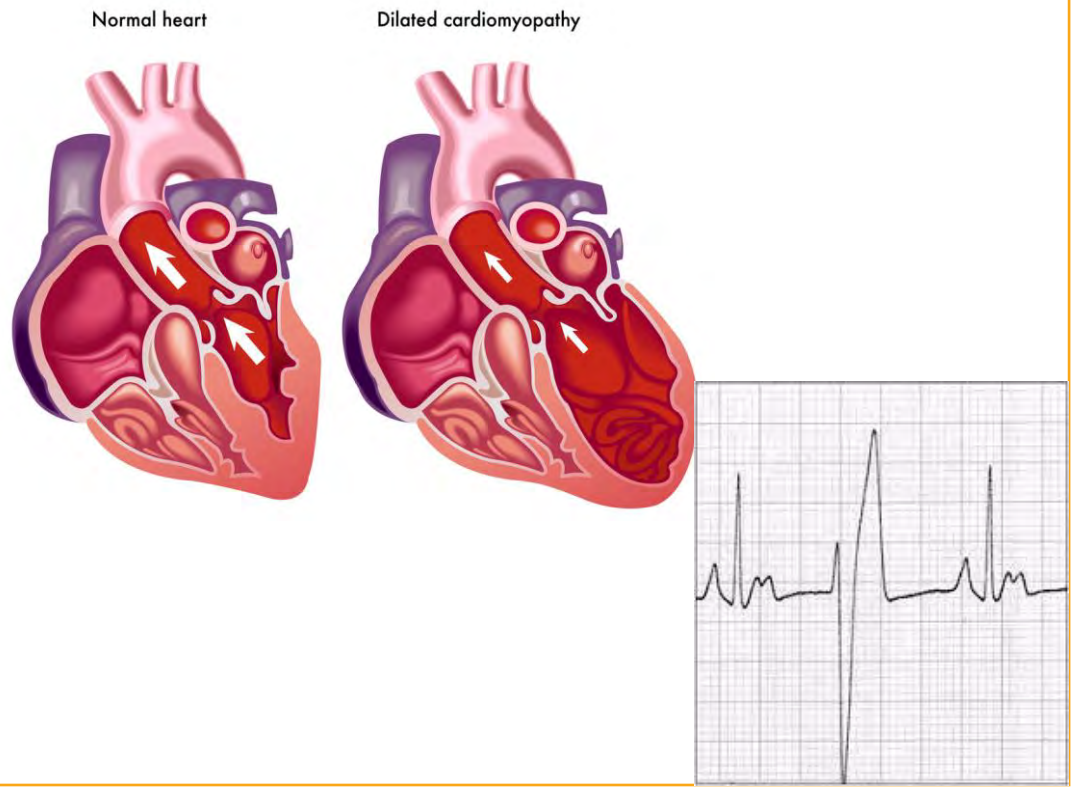


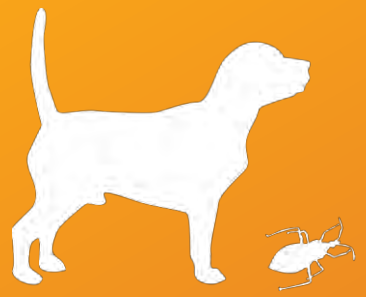
Chagas Disease

Pathogenesis

Progressive fibrosis and heart failure

- Bilateral ventricular failure and dysfunction (Myocardial dysfunction)
- Arrhythmias (conduction system failure)
- Extensive cardiac ventricular remodeling





Clinical Presentation

What do I see

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Chagas Disease

Clinical Symptoms Canine

Acute

Intense parasitemia

High grade tissue parasitism

Collapse

Arrhythmias/pericardial effusion

Lymphadenopathy

Neurological signs

Death

Mild, transient symptoms (ADR)

Chronic

Low grade intermittent parasitemia

Slow, progressive fibrosing myocarditis

ARRHYTHMIAS

Mitral and Tricuspid insufficiency

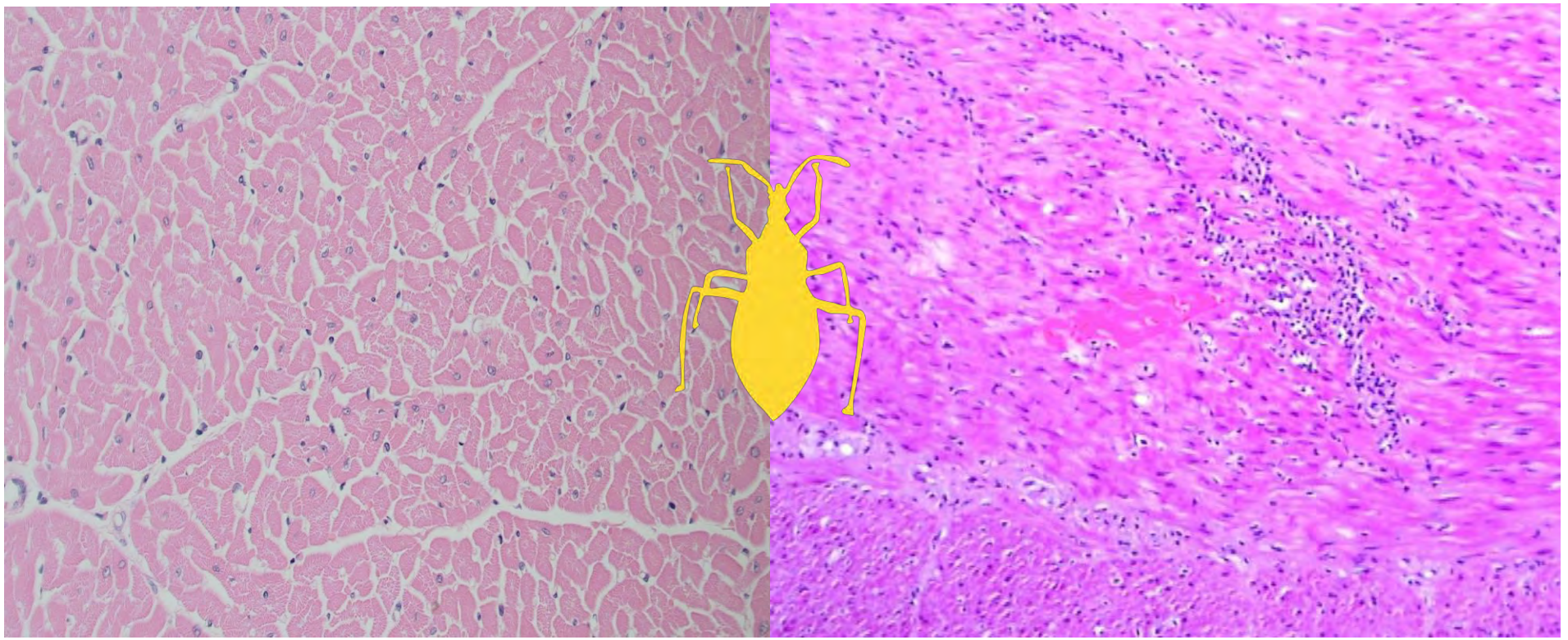
DCM (yep, even Dobies and Boxers)

Acute death

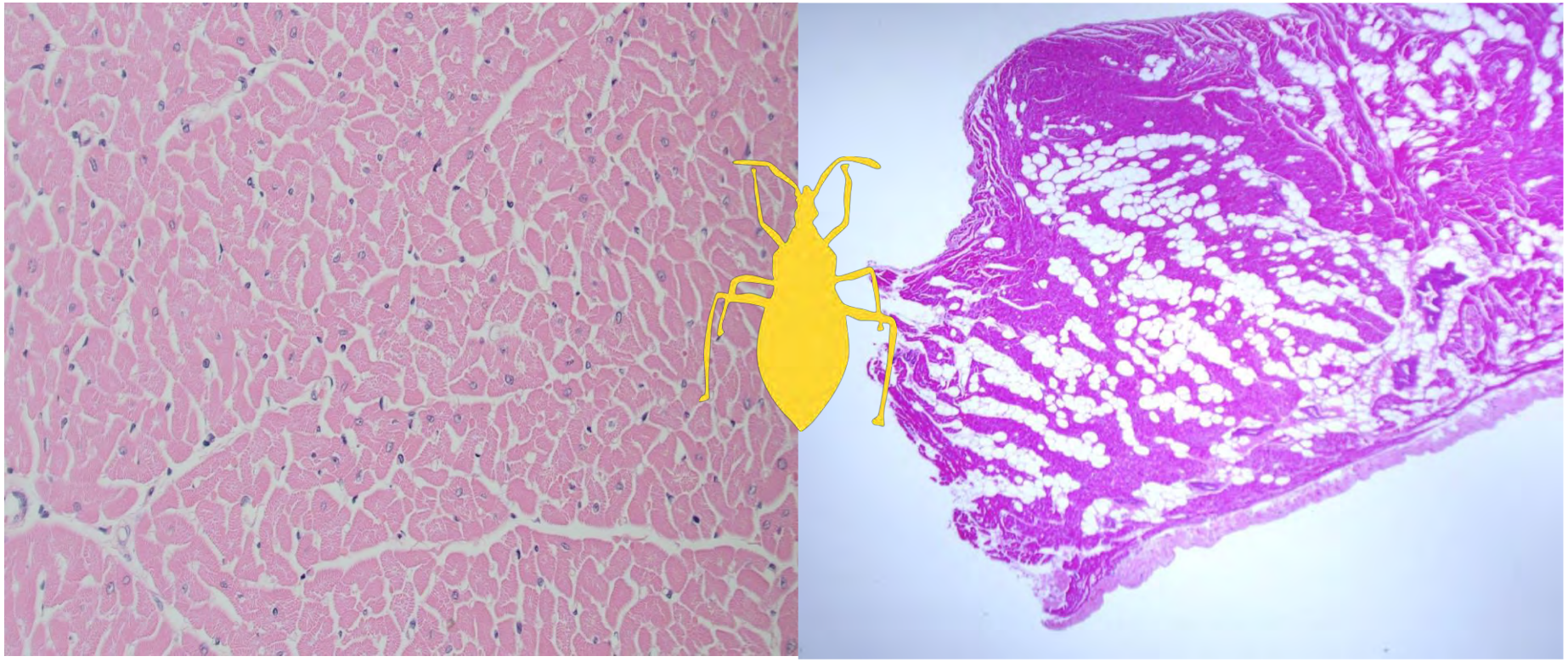
Food associated Cardiomyopathy

ASYMPTOMATIC

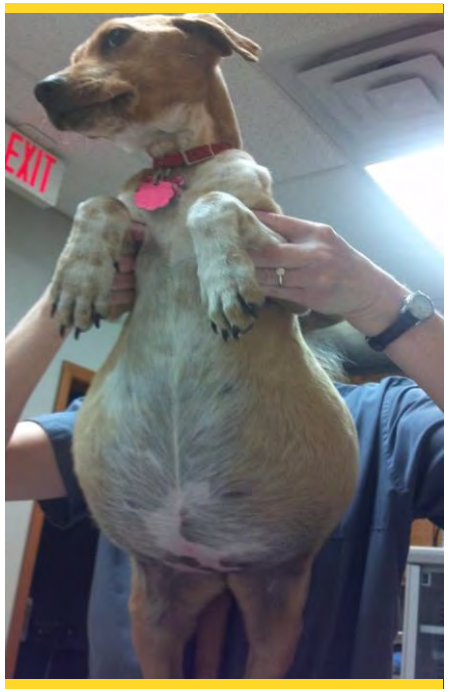
Chagas Disease



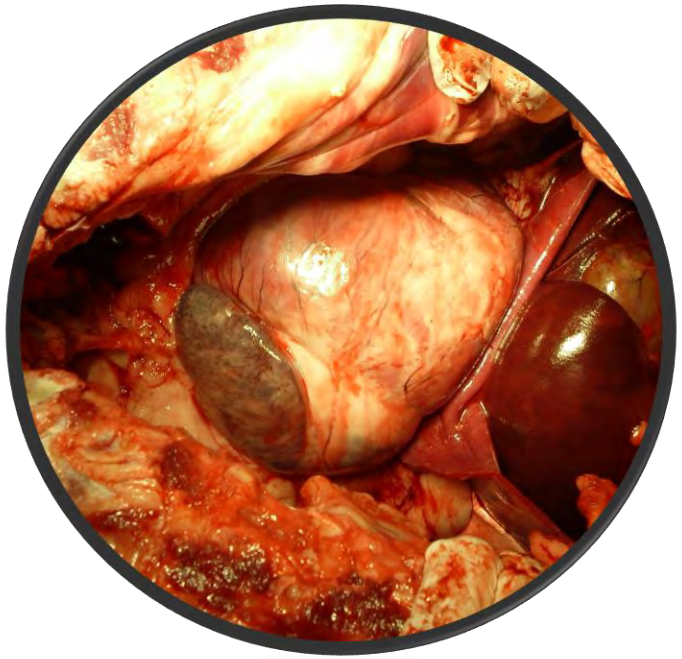
Chagas Disease



Chagas Disease



Chagas Disease



Chagas Disease

Congenital Transmission/Presentation

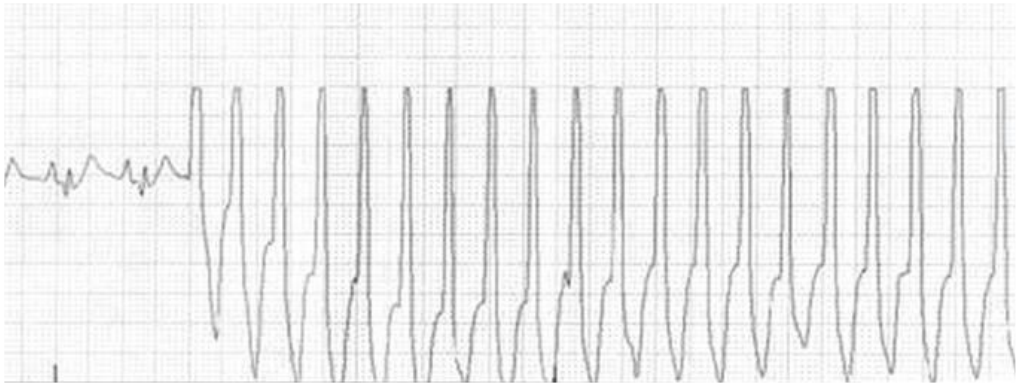
- Transmission in humans ~5%
- Treatment of mother
  - Reduces parasitemia
  - Reduces neonatal mortality and morbidity
- Canine
  - Unknown transmission rate
  - Data: Four puppies were born and after weaning had weakness, progressive weight loss, and chronic diarrhea. Necropsy of all four showed digestive alterations and cardiac dilation.
  - Acute death
  - Failure to thrive

Trypanosoma cruzi connatal transmission in dogs with chagas disease: Experimental case report. Vector-Borne and Zoonotic Diseases ***2011 Rodriguez-Morales et al***

Chagas Disease

Mortality Rate

- Profound
  - **35-40%** Kjos SA *Distribution and characterization of canine Chagas disease in Texas. Vet Parasitol. 2008*
  - **38%** Madigan R *Investigation of a combination of amiodarone and itraconazole for treatment of American trypanosomiasis (Chagas disease) in dogs JAVMA 2019*
  - **42%** Gavic EA *Trypanosoma cruzi infection diagnosed in dogs in nonendemic areas and results from a survey suggest a need for increased Chagas disease awareness in North America JAVMA 2023*
  - **25%** Alves O *Resting and Dynamic Electrocardiography in Dogs with Experimental Chagas Cardiomyopathy Epidemiology Research International 2012*



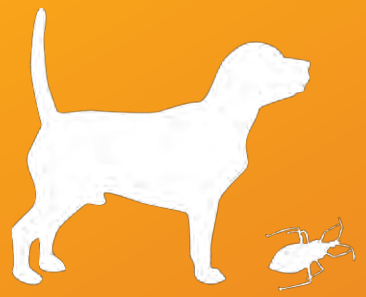
- Higher mortality rate than humans
  - **20-30%** develop heart disease
  - **15-20%** develop GI symptoms
  - **10-15%** die suddenly

  Maguire JH *Trypanosoma, Infectious diseases, 2004*

Chagas Disease

Who Do I test?

- **Cardiac patients**
  - Start Here!
  - MVD
    - Papillary muscle dysfunction from myocarditis and ischemia
  - DCM
    - 28% of dilated/systolic dysfuntion hearts have Chagas (Meyers 2019)
  - CHF
    - 40% of CHF have Chagas (Meyers 2019)
  - Right sided dilation/failure
  - Arrhythmias
  - Diet related
  - HCM – feline
- **Idiopathic (insert disease here)**
  - ITP/IMHA
  - Megesophagus
  - Brain/neurological disease
  - Uveitis
  - Splenomegaly



Diagnostics

Chagas Disease

ECG

Range of arrhythmias

Arrhythmogenic antibodies

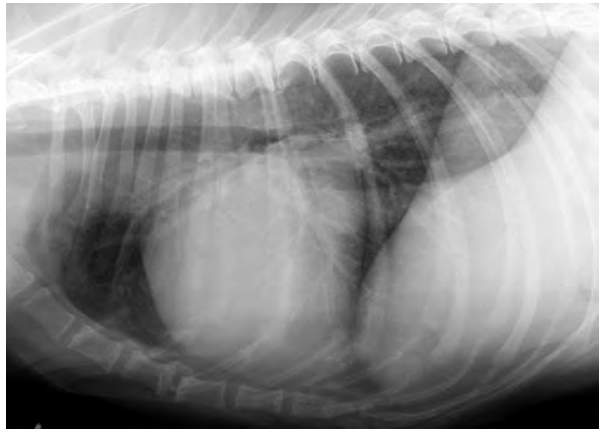
Autonomic denervation

Holter

Diagnostic Imaging

Radiographs

Echocardiogram



Pathology

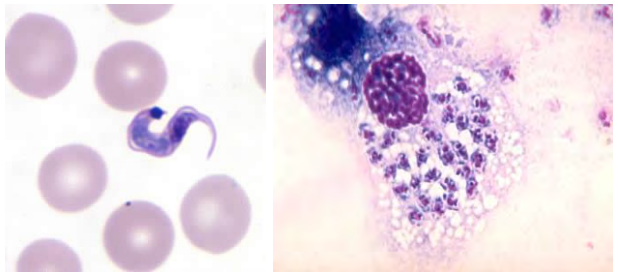
Blood smear

Troponin

White blood cell count

Lymph node aspirates

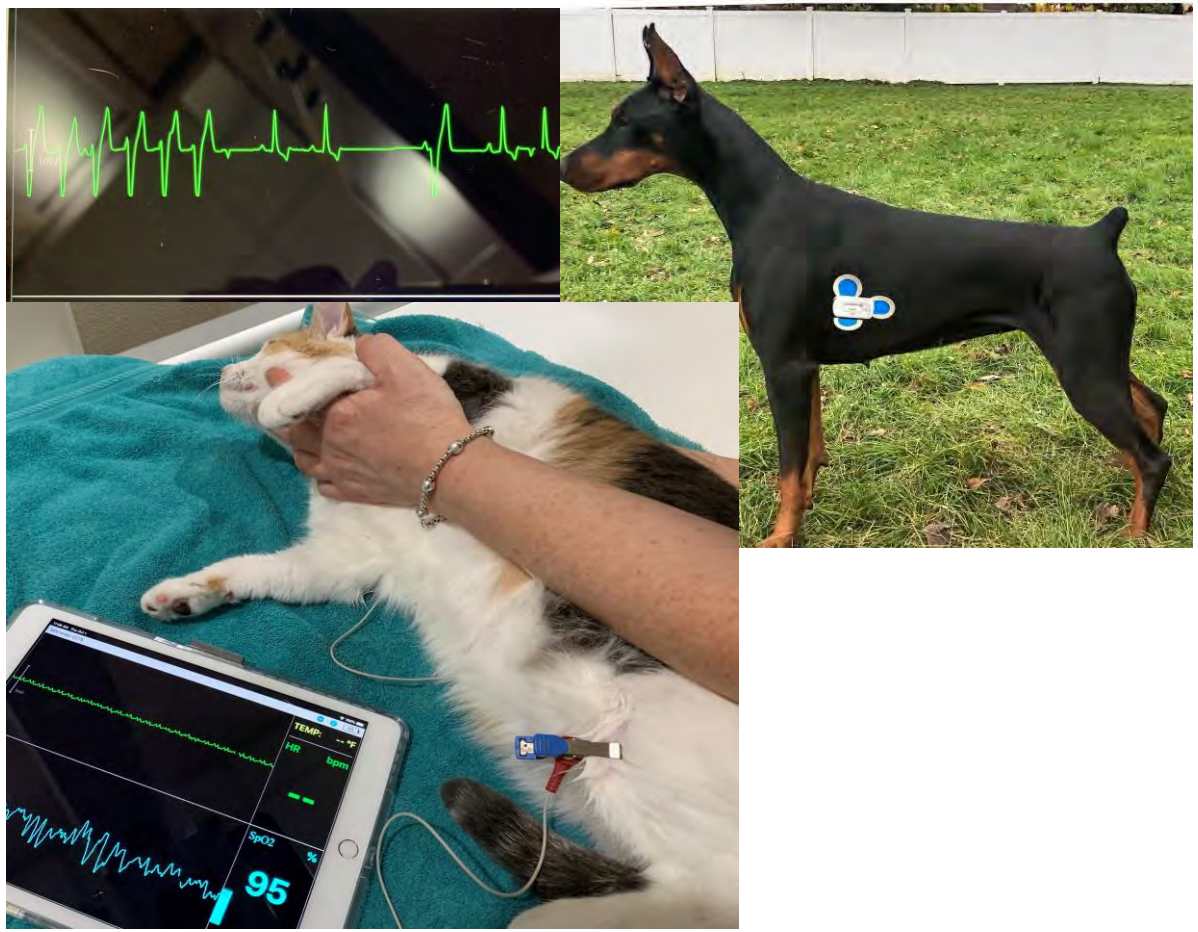
Necropsy



Chagas Disease

ECG is CRITICAL

- Pretreatment assessment
  - Common arrhythmias 80%
    - VPC
    - Heart block (AV)
    - ST segment depression
    - Sinus arrhythmia
    - Holter
- Follow during treatment
  - Should resolve after first month
  - Consider mexiletine adjunct
- Post treatment
  - Lifelong antiarrhythmic



Chagas Disease

Diagnostics

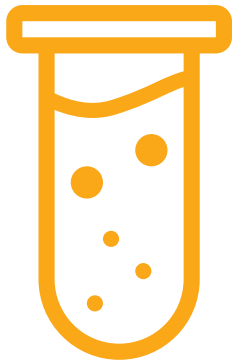
- Serology (21 day post infection)
  - **IFA** (70% sen/ 90% spc)
    - *Lifelong persistence likely*
    - *Texas Veterinary Medical Diagnostic Laboratory*
  - **ELISA** (90% sen/100%spc)
    - *Less cross reactivity*
    - *More sensitive*
    - *Recommended single test*
    - *GOLD standard*

PCR

- Kinetoplast DNA 121/122
- 99%+ Acute sensitivity, 100% specificity
- 51% Chronic sensitivity, 100% specificity
- Decreased parasitemia with chronicity of infection
- Serial PCR - Good for monitoring treatment efficacy

Blood Culture

- Slow (2-20 weeks)
- Limited Use

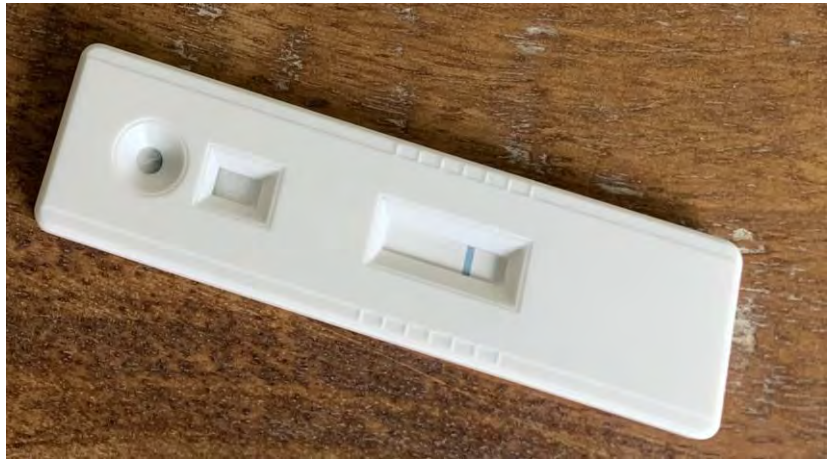


Chagas Disease

Diagnostics

- **ELISA**
  - More sensitive 90%
  - Currently available VRL ($125)
  - Soon at reference lab
  - Better than IFA

- **Lateral Flow (LFA)**
  - Accurate (sensitive 96%/specificity 100%)
  - Rapid (10 minutes)
  - Cheap (~$35)
  - Paired option with Heartworm
  - Available 2024



Chagas Disease

IFA Performance vs. ELISA (Real World Data)		
Serum Sample (Animal ID)	VRL ELISA	TVMDL IFA
Echo	Positive	Negative
Lyric	Positive	Negative
Marley	Positive	Negative
Midnight	Positive	Negative
Mila Rose	Positive	Negative
Blue	Negative	Negative
Hunter Costilla	Negative	Negative

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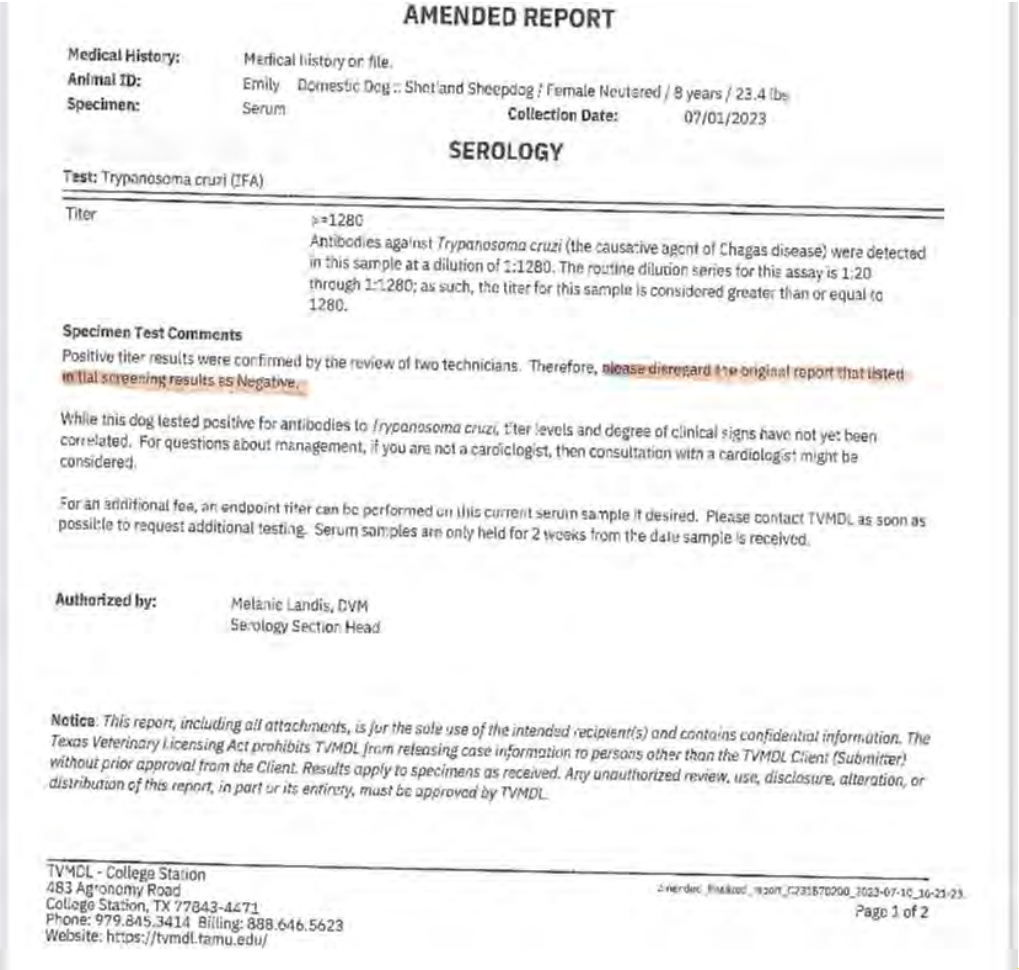

AMENDED REPORT

Medical History: Medical history on file.
Animal ID: Emily Domestic Dog :: Shetland Sheepdog / Female Neutered / 8 years / 23.4 lbs
Specimen: Serum **Collection Date:** 07/01/2023

SEROLOGY

Test: Trypanosoma cruzi (IFA)

Titer >=1280
Antibodies against *Trypanosoma cruzi* (the causative agent of Chagas disease) were detected in this sample at a dilution of 1:1280. The routine dilution series for this assay is 1:20 through 1:1280; as such, the titer for this sample is considered greater than or equal to 1280.

Specimen Test Comments
Positive titer results were confirmed by the review of two technicians. Therefore, please disregard the original report that listed initial screening results as Negative.

While this dog tested positive for antibodies to *Trypanosoma cruzi*, titer levels and degree of clinical signs have not yet been correlated. For questions about management, if you are not a cardiologist, then consultation with a cardiologist might be considered.

For an additional fee, an endpoint titer can be performed on this current serum sample if desired. Please contact TVMDL as soon as possible to request additional testing. Serum samples are only held for 2 weeks from the date sample is received.

Authorized by: Melanie Landis, DVM
Serology Section Head

Notice: *This report, including all attachments, is for the sole use of the intended recipient(s) and contains confidential information. The Texas Veterinary Licensing Act prohibits TVMDL from releasing case information to persons other than the TVMDL Client (Submitter) without prior approval from the Client. Results apply to specimens as received. Any unauthorized review, use, disclosure, alteration, or distribution of this report, in part or its entirety, must be approved by TVMDL.*

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Chagas Disease

IFA Limitations

- **Sensitivity Decline**
  - 2015 – present
    - 2-4x drop in cases
  - Unexplained (officially)
  - Strain type discrepancy
    - Using unknown species T cruzi
    - Whole epimatigote
- **Impact**
  - Significant false NEGATIVE results
  - Discrepant results
    - Subsequent IFA tests “serorevert” spontaneously
    - Low initial positive titers
  - High morbidity/mortality in patients
  - Premature discontinuation of treatment
  - Misdiagnosis (“diet” cardiomyopathy)

Variable	Sample size, no. (%)	Positive *T. cruzi* infection, no. (%)
Year		
2010	60 (16.1)	14 (23.3)
2011	59 (15.7)	10 (16.9)
2012	42 (11.2)	7 (16.7)
2013	48 (12.8)	13 (27.1)
2014	57 (15.2)	11 (19.3)
2015	56 (14.9)	3 (5.4)
2016	53 (14.1)	5 (9.4)

Meyers et al 2019

Chagas Disease

Test Discrepancies

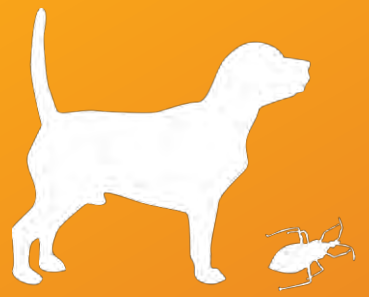
- False Negatives
  - Early infection
    - PCR + , Ab –
  - Strain type variation
  - Host immune response antibody variation
    - Test can't detect it
- False Positives
  - UNLIKELY
  - *T. rangeli; Leishmania spp*
  - Maternal Ab
  - ELISA / LFA/ PCR to rule out cross reactivity
  - Nonspecific Binding Proteins
- Can I trust the test?

"It is likely that many of the dogs seropositive with a single Test [LFA] were not false positives but indeed infected with T. cruzi." *Elmayan et al 2019*

Chagas Disease

Monitoring

Chih-Ling Zao, Ph.D.
Chief Scientific Officer
VRL-San Antonio
7540 Louis Pasteur, Suite 250
San Antonio, TX 78229
Tel: 210-615-7275 option. 3
Email: chih-ling.zao@vrl.net



Treatment

Chagas Disease

Benznidazole

- Targets *T. cruzi* DNA via free radical generation
- Not FDA approved in dogs
- Difficult to obtain
- Humans:
  - Good efficacy in Acute phase (>90% efficacy)
  - Poor efficacy in Chronic phase (BENEFIT study)
  - Side effects common
- Dogs:
  - Very poor response in US strain I (0% efficacy)
  - BNZ/ITZ (2019). *Experimental Parasitology* (5% efficacy) Acute phase

Allopurinol

- Xanthine oxidase inhibitor (reduces uric acid)
- Humans 62% reduction in parasitemia
- Unknown efficacy in dogs via purine inhibition

Other Azoles

- Ketoconazole
- Fluconazole
- Posaconazole
- Ravuconazole

Vida Pharmacal

Chagas Disease Treatment

Amiodarone

- Class III antiarrhythmic
- Disrupts calcium homeostasis/Cruzipain
- Loading dose: **15mg/kg PO SID x 28 days**
- Maintenance: **7.5mg/kg PO SID**
- Adverse events: ALT/SAP elevations, lethargy, anorexia

Itraconazole

- Triazole antifungal
- Ergosterol inhibitor
- **5 mg/kg PO SID with food**
- Adverse events: anorexia, vomiting, weight loss, cutaneous eruption, ALT/SAP elevations, lethargy

Treatment is for 12 months

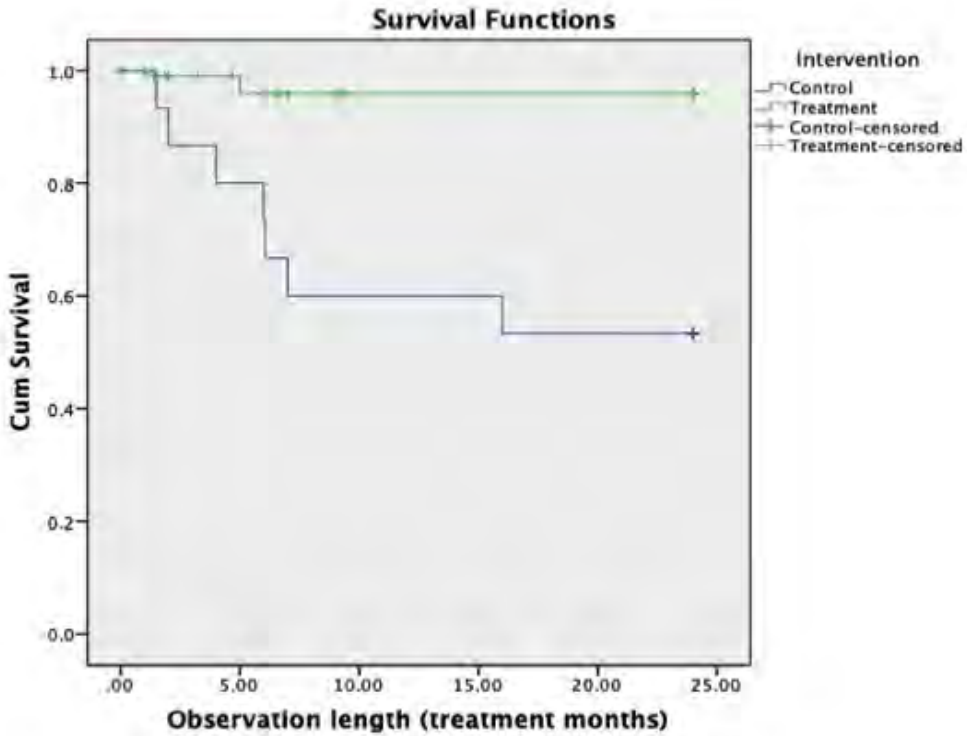
Chagas Disease

Treatment Efficacy

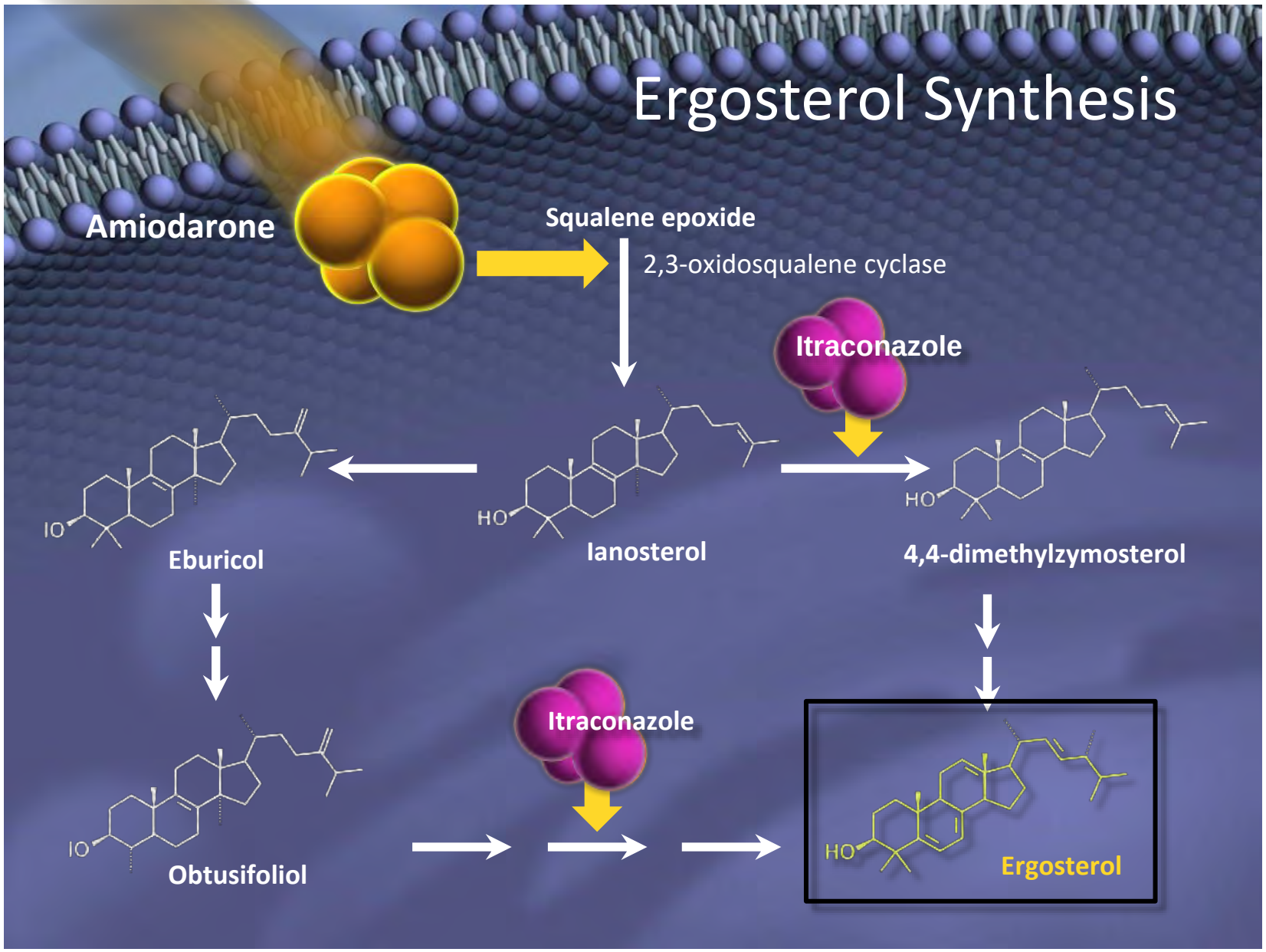
Data

Investigation of a combination of amiodarone and itraconazole for treatment of American trypanosomiasis (Chagas disease) in dogs; *JAVMA August 1, 2019*

- 16 Untreated / 105 Treated dogs
- 21 breeds ages 5d - 14 yr
- Complete suppression of Parasitemia
- Increased survival times
- 100% reversal of arrhythmias
- Clinical improvement 98% of treated dogs



Vida Pharmacal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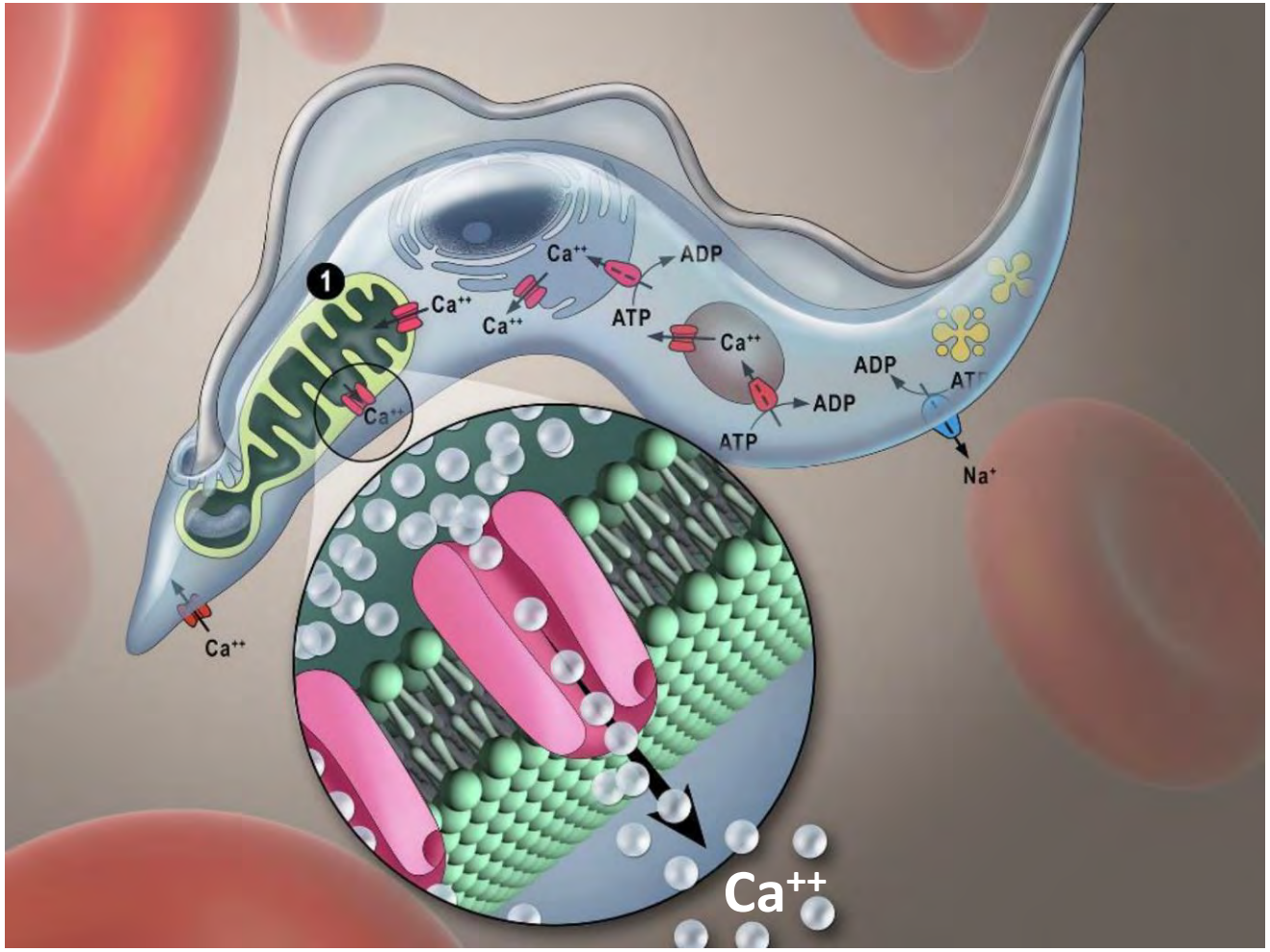
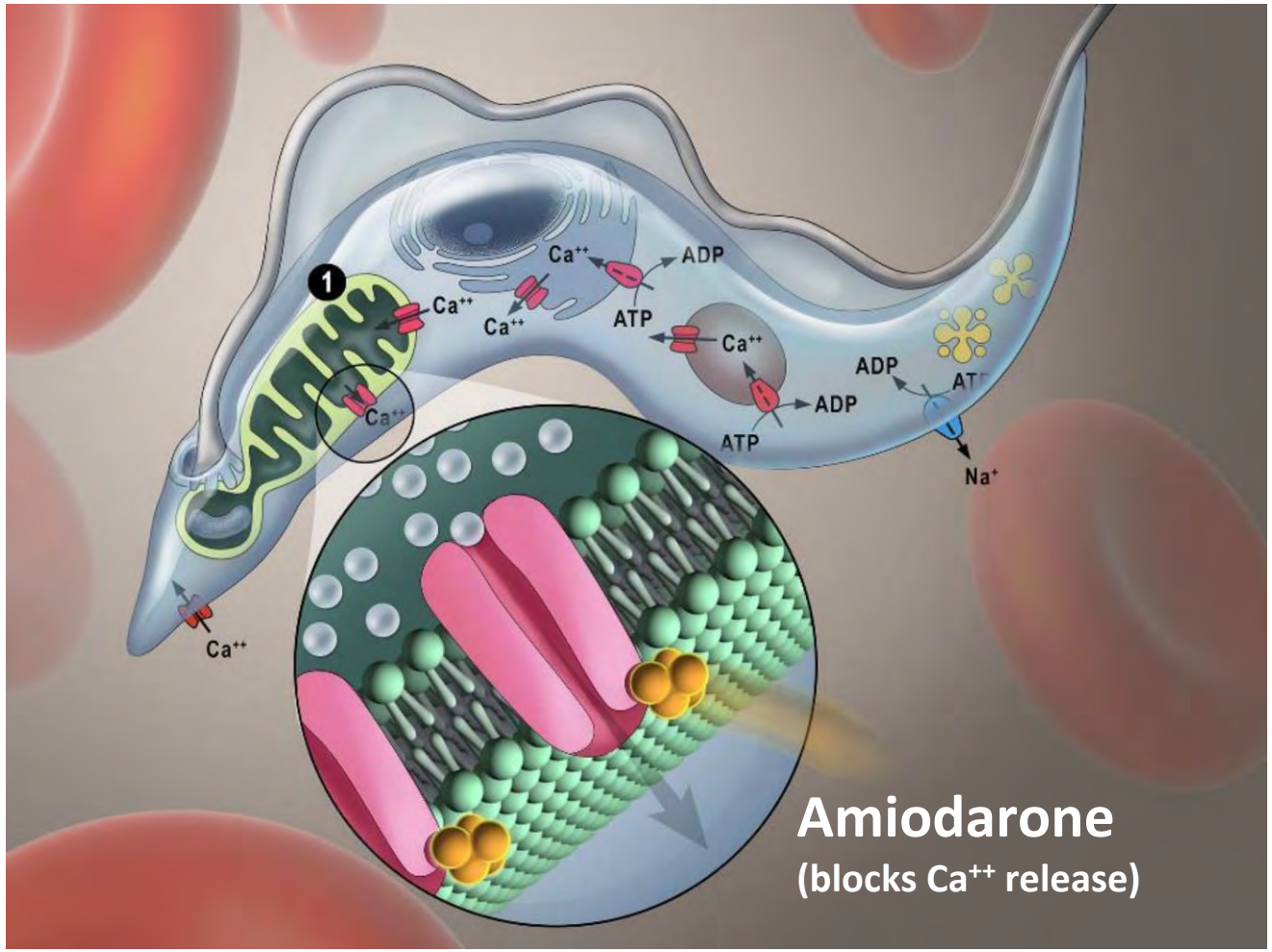
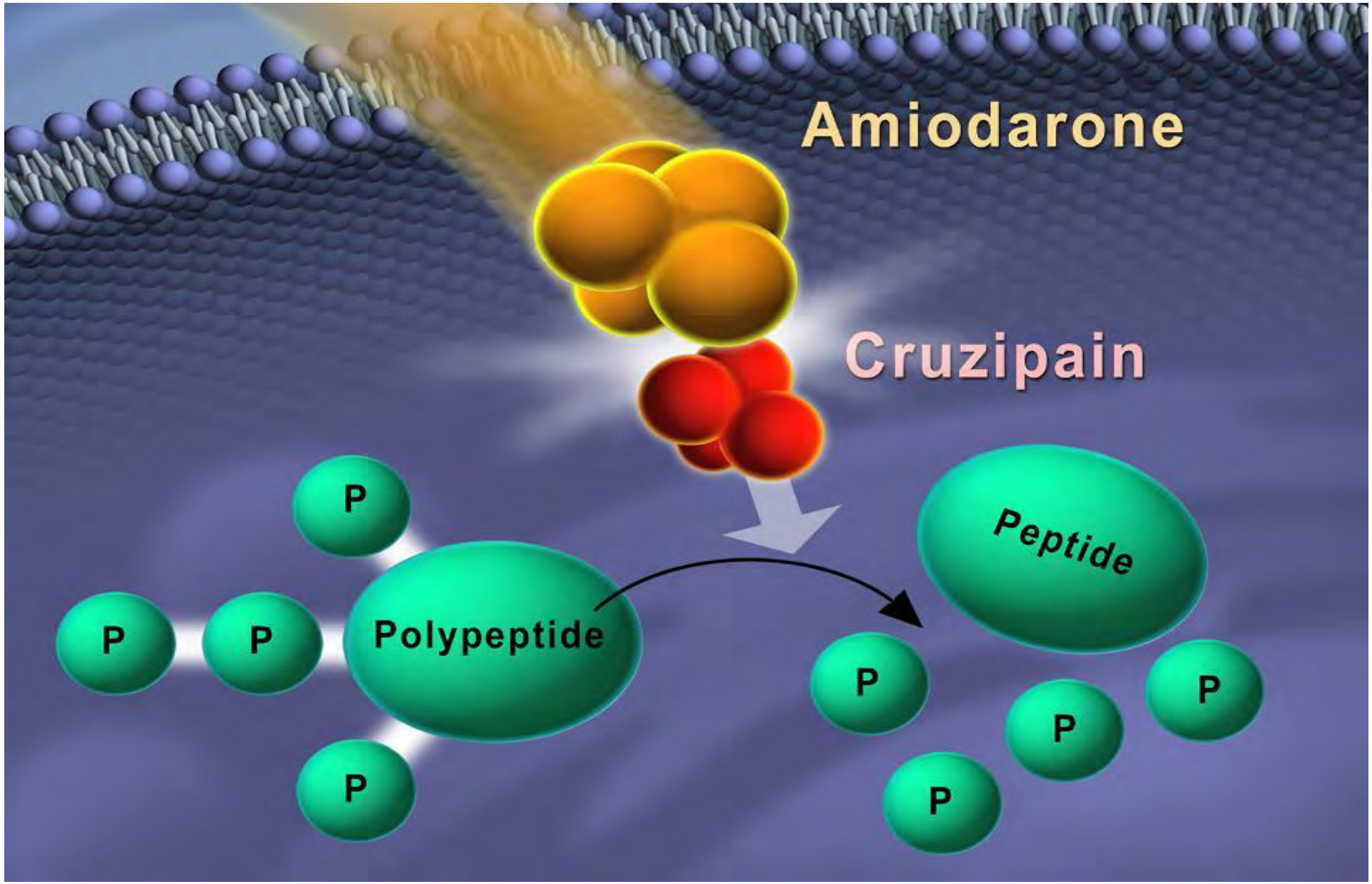
Amiodarone
Squalene epoxide
2,3-oxidosqualene cyclase
Itraconazole
HO
Lanosterol
HO
4,4-dimethylzymosterol
IO
Eburicol
IO
Obtusifoliol
Itraconazole
HO
Ergosterol

1-Kinetoplast



1-Kinetoplast

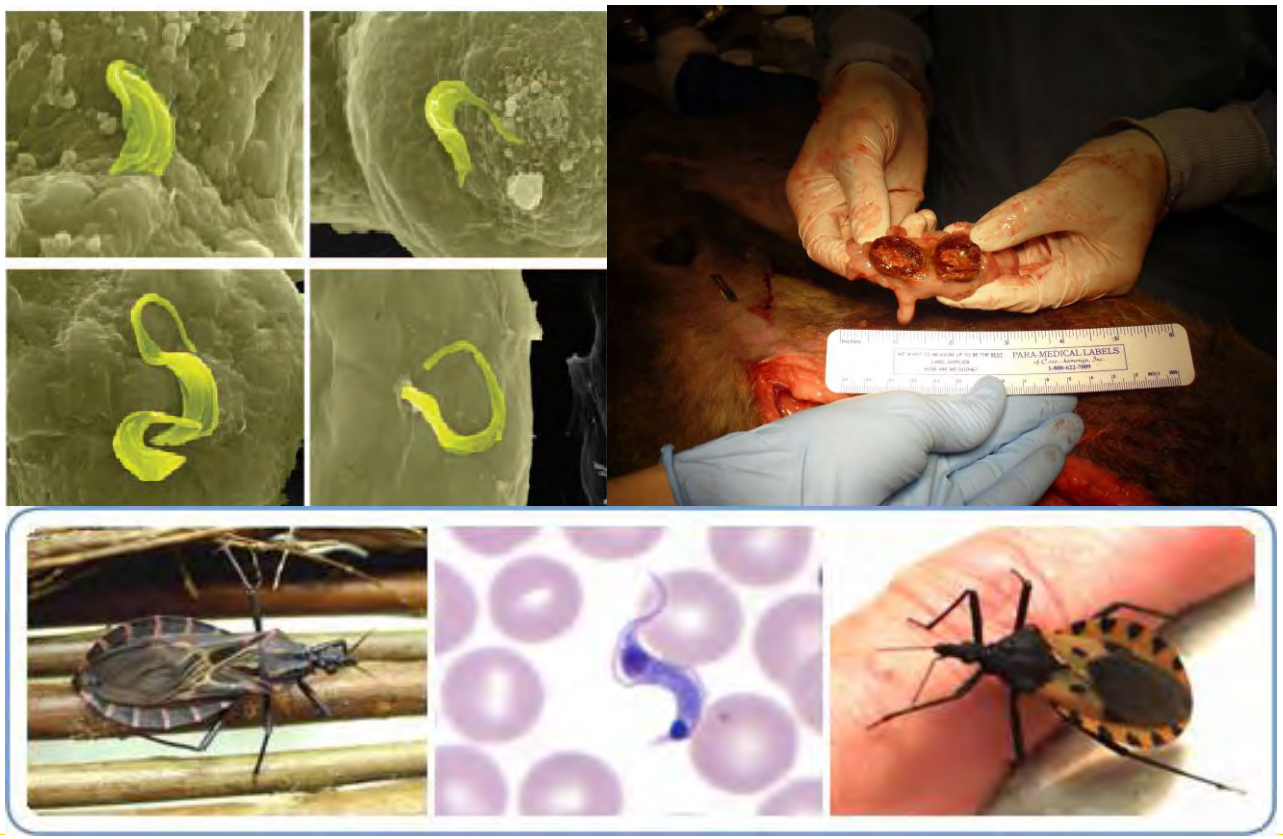



Amiodarone
Cruzipain
P
P
P
Polypeptide
P
Peptide
P
P
P
P

Chagas Disease

Why treat for 12 months?

- Privileged Sites
  - Fat, macrophages, heart
  - Intracellular
- Slow replication
  - Amastigote phase
- Down regulation of T cells
- Resiliant
  - Slows cell division in response to treatment (Dormancy)



Chagas Disease

Monitoring

Chagas Management

- Follow your patient
  - Adjust itraconazole dosage
    - Remember
      - Nonlinear plasma drug levels
    - Adjust by 50%
  - Amiodarone adjustment 50%
    - Won't reduce efficacy for cidal effects
    - WILL REDUCE anti-arryhthmic
  - Recheck itraconazole/Chem-7 if abnormal
  - 1 Year follow-up
    - Stop medication 1 year
    - PCR 30 days after treatment stop
    - PCR 60 days after treatment stop*
    - ECG if pretreatment abnormal

MONTH	PLAN
1	Recheck exam/Itraconazole level/Chem-7/ECG
12	Discontinue treatment
13	Recheck exam/PCR #1/ECG
14	Recheck exam/PCR #2

Itraconazole level target: 1.5-3.0 ug/mL (HPLC) *Bioassay, if used, should be 25% higher.* This test is at TVMDL (979-845-3414) or Auburn university (334-844-7187)

*Alternatively, PCR #1 and #2 can be run on the same day at two distinct time points i.e. AM / PM

Chagas Disease

Supportive Care

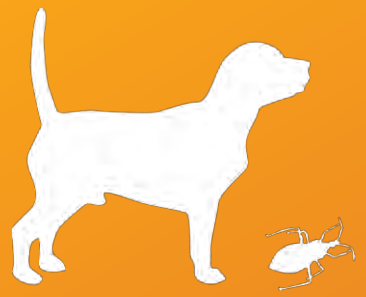
Quadruple therapy

1. ACEi
- Enalapril or Benazepril

2. Pimobendan

3. Furosemide/Torsemide
- Renal caution

4. Spironolactone
- RAAS inhibition
- Reduction of fibrosis



Environmental Control

Reduce Infections

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Chagas Disease

Environmental Control

Environmental Control

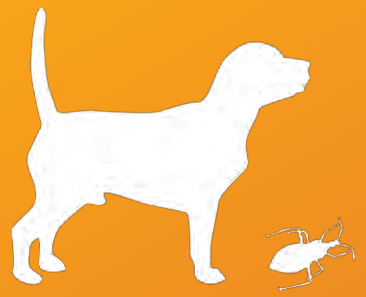
- Permethrin
- *Cypermethrin*

Systemic Control

- Isoxazolines
  - *Fluralaner* (Bravecto®)
  - *Afoxolaner* (NexGard®)
  - Rapid triatomine death within 5 days
    Bonus: phlebotomine sandflies

Systemic insecticide treatment of the canine reservoir of Trypanosoma cruzi induces high levels of lethality in Triatoma infestans, a principal vector of Chagas Disease

Loza et al. Parasites & Vectors (2017) 10:344



Case Study

Remi

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Chagas Disease

Case Study

Remi

9 Y neutered Labrador Boerne, TX

- Emergency clinic: Lethargy, tenesmus, diarrhea. FAST scan WNL except scant pericardial effusion
- Arrhythmia
- Diarrhea (self limiting)
- HR: 160bpm irregular
- 3/6 systolic murmur L
- Rectal: wnl
- **Chagas IFA**: Negative
- **Chagas ELISA**: Positive

Chagas Disease

Case Study

Remi

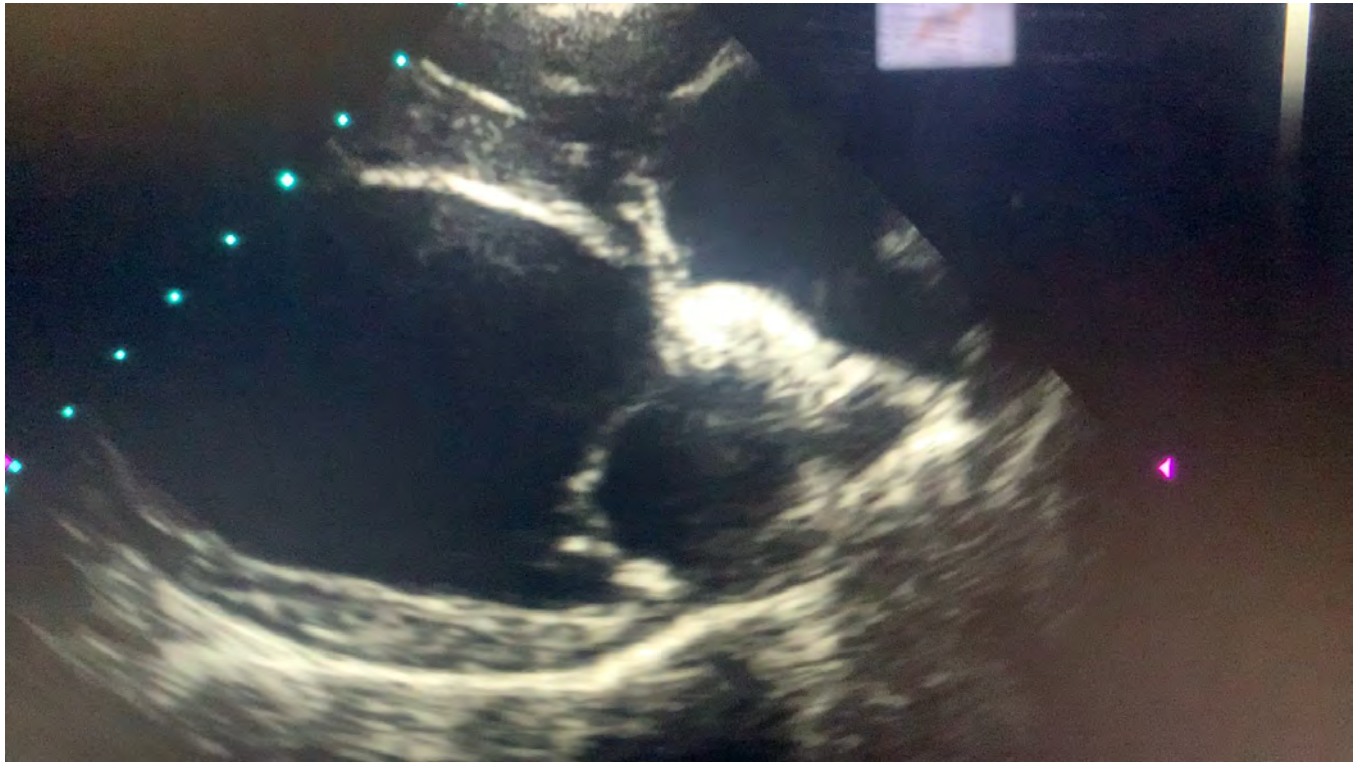
- **Thoracic radiographs**
  - Dilated heart
  - LA/LV
- **Echocardiogram**
  - Atrial and ventricular enlargement
  - Poor function
- **Holter monitor**
  - Premature atrial contractions
  - Sinus arrhythmia
- **Chagas PCR**: negative

Chagas Disease

Case Study

Remi

- **Decreased function**
  - Left ventricular enlargement
    - LVIDs: 44.3 (<25mm)
    - EPSS: 13 (<8mm)
    - Poor contractility
- **Left and Right atrial enlargement**
  - La:Ao 1.75 (<1.6)
- **Pulmonary artery dilation**
  - MPA:Ao: 1.25 (<1.0)
  - Mild Pulmonary hypertension



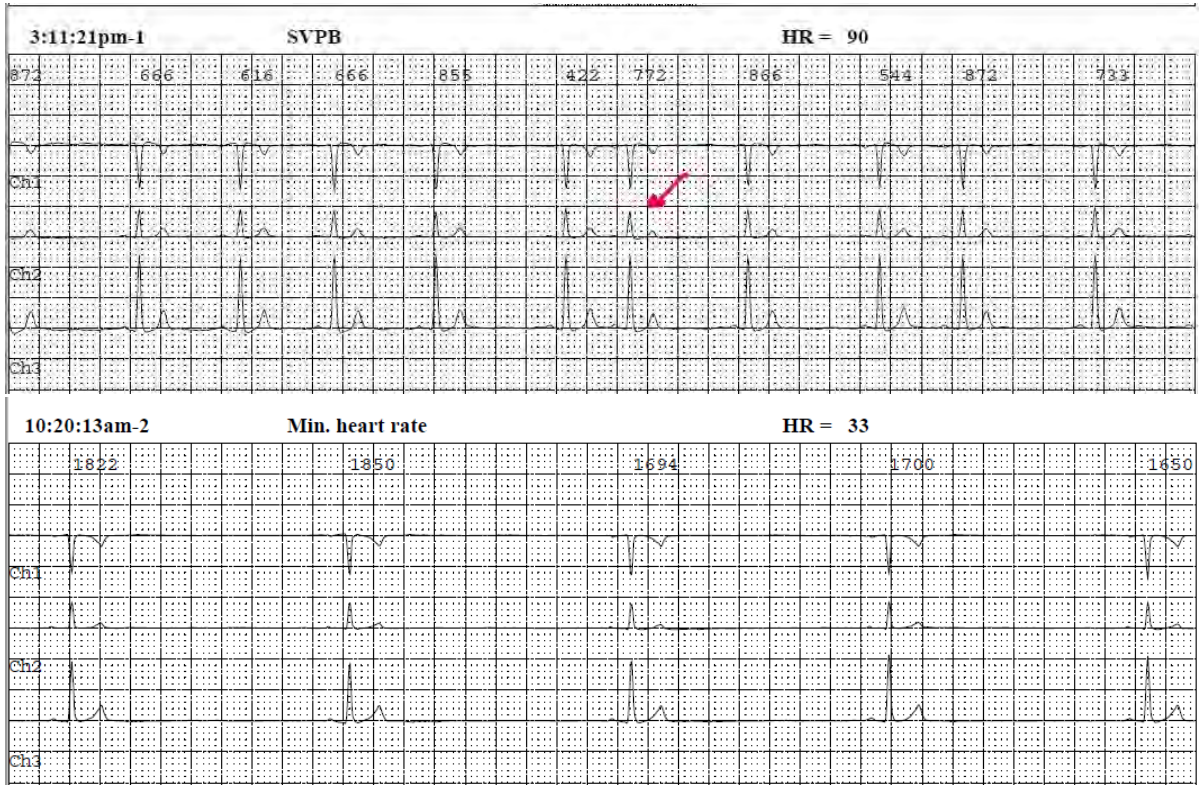
Chagas Disease

Case Study

Remi

- **Premature atrial contractions**
  - Atrial irritability

- **Bradycardia**
  - Profound (40% of total beats)
  - 33 bpm minimum
  - Neurotropic effect of *T cruzi*
    - Affinity for parasympathetic ganglia
    - Disruption of Autonomic Nervous System

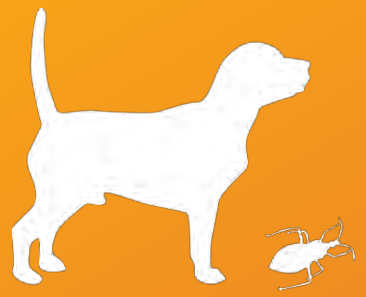


Chagas Disease

Case Study

Remi

- **Treatment**
  - Pimobendan 0.25mg/kg TID
    - Reduce afterload/preload
    - Increase contractility
  - Tadalafil 1-2mg/kg SID
    - Arterial dilation
  - Amiodarone/itraconazole
  - Patient had immediate, profound improvement within 24 hours
- **Day 28 Recheck**
  - ECG
  - Liver panel, Itraconazole level



Case Study

Turbo

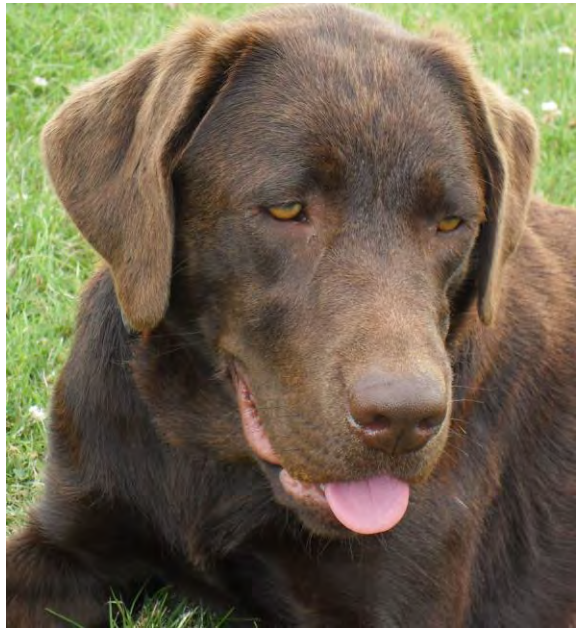
Vida Pharmacal

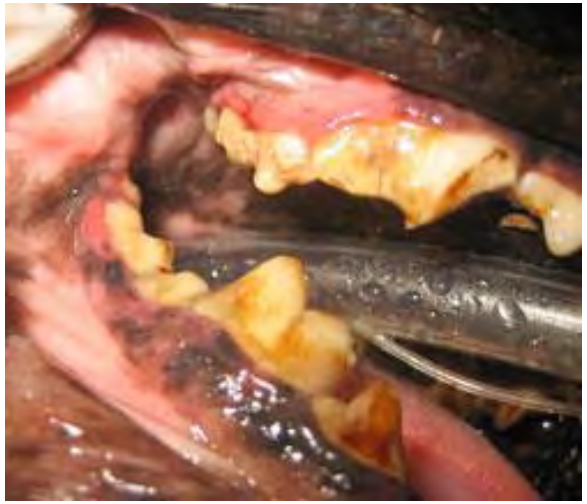
Chagas Disease

Case Study

Turbo

- 12 y/o, N Labrador Retriever
- Indoor/outdoor
- San Antonio TX
- PE: periodontal disease II/IV
- Preop: WNL
- P: Dental prophylaxis





Chagas Disease

Case Study

Turbo

- ECG: VPCs, single, uniform

- Represent ectopic impulses which originate from the ventricular myocardium
  - Caused from reduced myocardial O2 and inflammation
- Stable BP/ spO2
- Good recovery from anesthesia

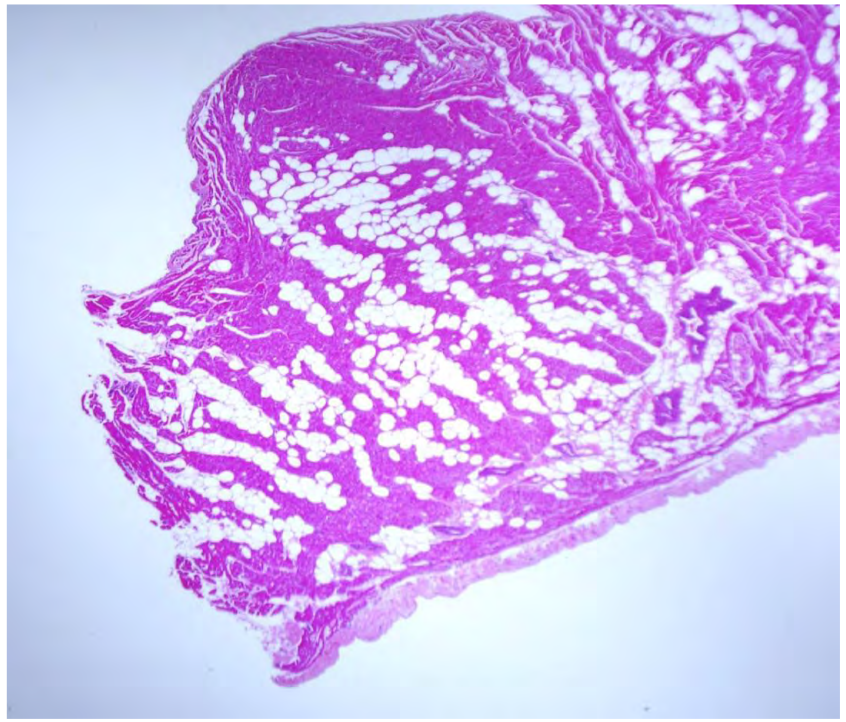
Chagas Disease

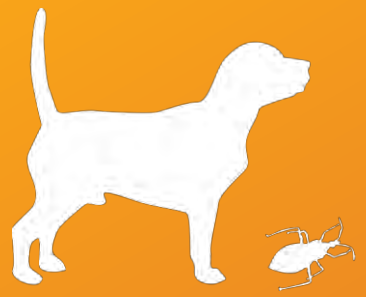
Case Study

Turbo

Treatment

- Amiodarone/itraconazole X 365 d
- Meloxicam SID x 30 days
    - Reduction of fibrosis
- Vector control
- PCR
    - Negative for 2 consecutive samples
- Resolution of VPCs
- Euthanized 1.5 yr later spinal stenosis
- Severe fibrosis/fat cardiac





Case Study
Princeton

Vida Pharmacal

Chagas Disease

Case Study

Princeton

- Asymptomatic; wellness check, other packmates + Chagas
- Physical exam WNL; CBC/Chem7 WNL; Chagas IFA(-)
- 8 weeks later: 4 grand mal seizures
- CBC/Chemistry/Toxoplasma/Neospora/RMSF/Chagas/Thoracic radiographs/ECG:
  - Mature neutrophilia 18,000 (<16k)
  - T cruzi IFA + 1:320
  - ECG: sinus rhythm
- Neuro consultation: WNL
- MRI: “collection of fluid is seen what appears to be within the parenchymal margin”

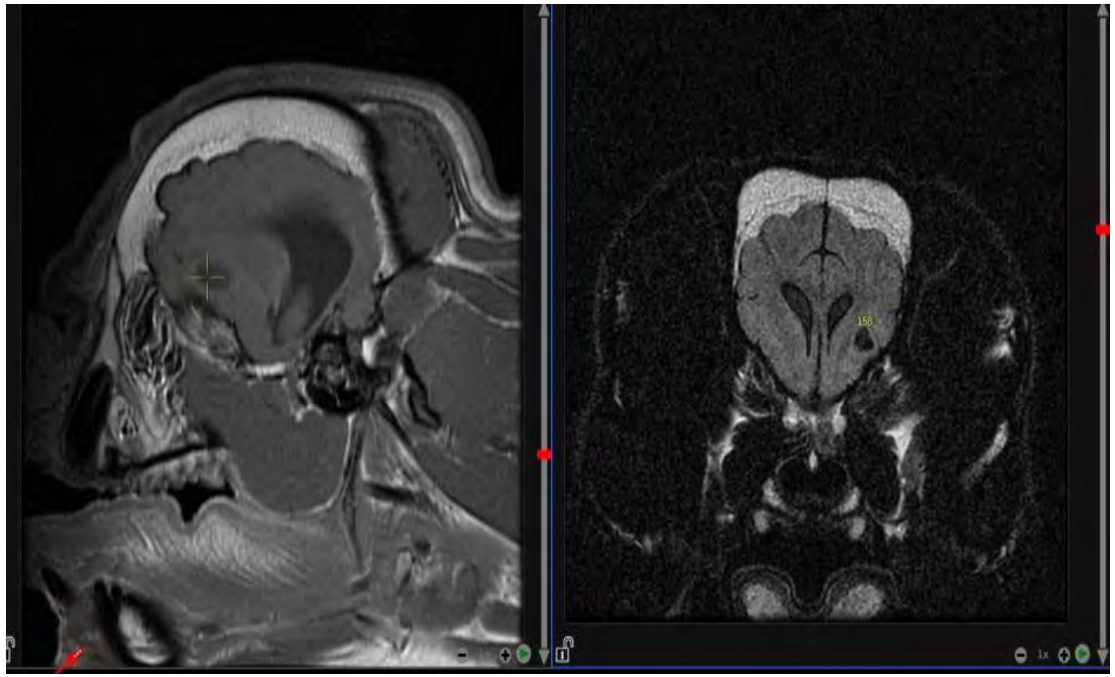
Chagas Disease

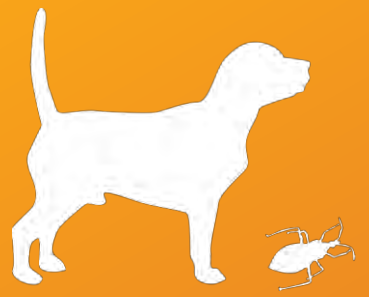
Case Study

Princeton

MRI:
“The constellation of findings and reported history of seizures may be consistent with a prior necrotizing encephalitis or a resolved parenchymal lesion with a resulting fluid pocket replacement in the region of a portion of the brain parenchyma or sulcus on the right.”

- Treatment
  - Zonisamide 10mg/kg PO BID
  - Itraconazole/amiodarone
- Follow-up
  - 6 months into treatment (May 2022)
  - Seroreversion to NEGATIVE
  - Zonisamide longterm
    - He has a hole in his brain!





Chagas Registry

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Chagas Disease

Registry

Registry Prevalence Rates			
Week Ending : 9/15/2023			
	Total Dogs Tested	# Positive Dogs	Prevalence
All Registry enrolled dogs	2318	710	30.6%
Practices that test all dogs for Chagas	577	80	13.9%
Practices that test only symptomatic dogs for Chagas	1741	630	36.2%

Chagas Disease

Registry

THANK YOU

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