

# Zoonotic Infections in Indian Country

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# Case History

- ❖ The patient is a 35 year old man who presented to a clinic in the Southwest complaining of severe right hip pain of 24 hours duration. He has been staying in a hogan at his family's sheep camp in the mountains. He has had marked myalgias and fever at home. He complains of headache and chills.





# Case History

- ❖ On physical examination the patient appears very toxic with a fever of 104 degrees F, blood pressure of 92/46 and heart rate of 124. His hip is flexed and he has severe pain with motion. You feel marked tenderness and induration in the right groin overlying the hip. The nurse hands you the CBC report: WBC 19K (85%P, 13% B, 2%L), Hct 47% and Platelets 175.





# Differential Diagnosis

- ❖ Plague
- ❖ Rocky Mountain Spotted Fever
- ❖ Acute HIV Infection
- ❖ Tularemia
- ❖ Group A Streptococcal suppurative adenitis

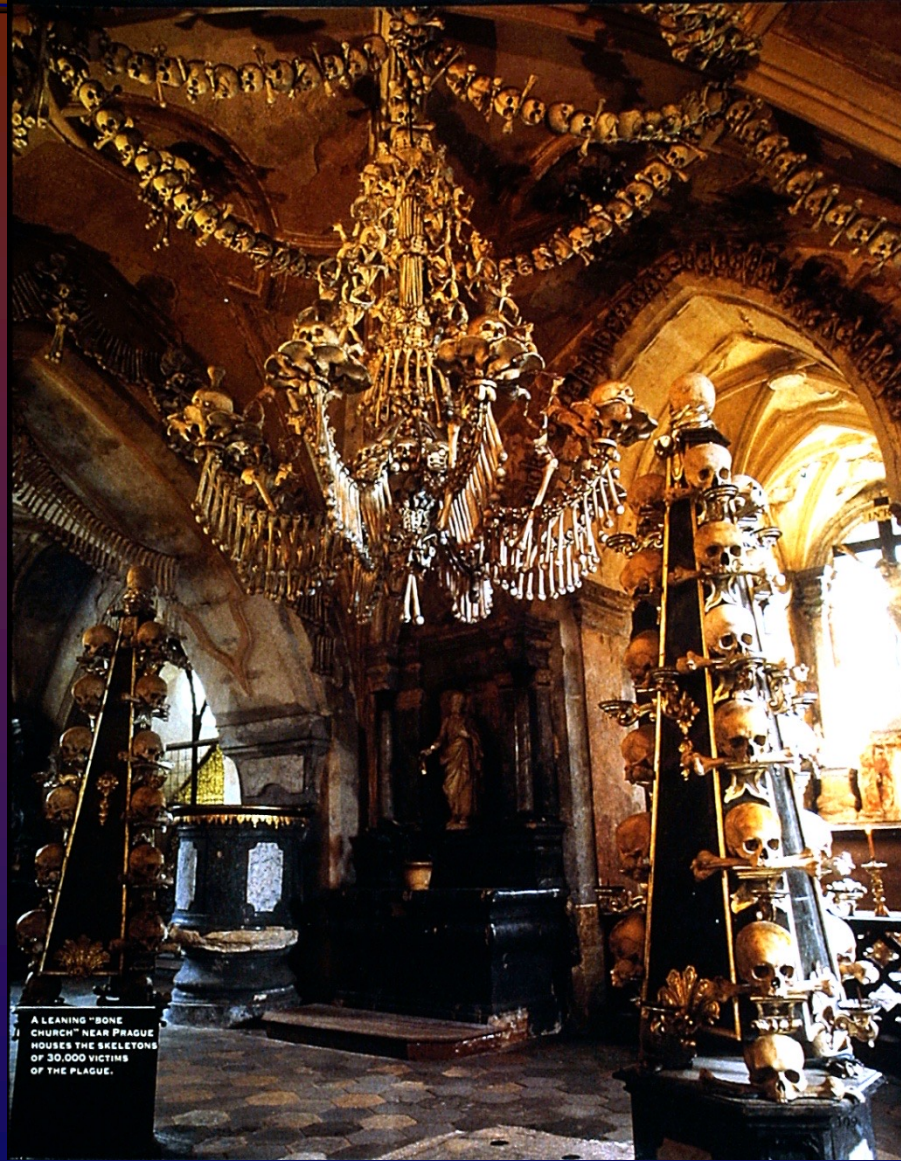






# Plague History

- ❖ First reported in the world's medical literature among the Philistines (*Zabud et al*, the Bible, 1320 BC)
- ❖ 100 million deaths in Europe in 542 AD during the reign of Justinian
- ❖ The Black Death pandemic of 1347 led to 25 million death
- ❖ Alexander Yersin discovers the bacillus 1894



A LEANING "BONE CHURCH" NEAR PRAGUE HOUSES THE SKELETONS OF 30,000 VICTIMS OF THE PLAGUE.





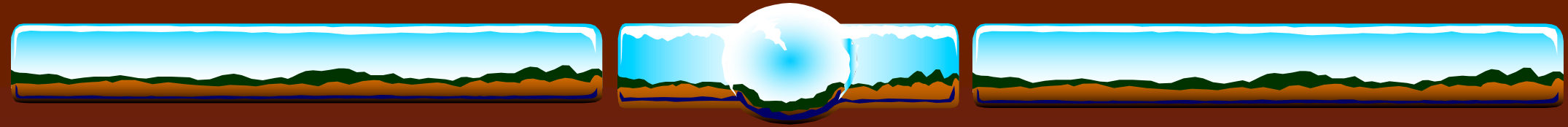
# Plague

## Epidemiology

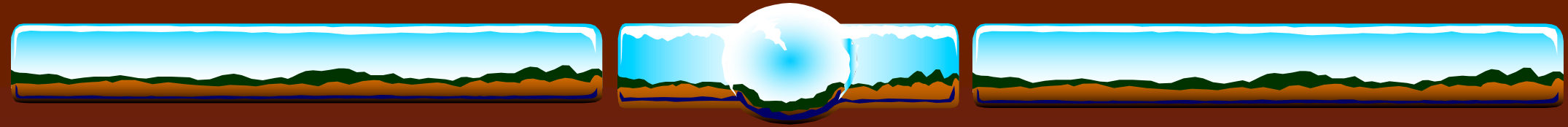
- ❖ Enzootic worldwide in small mammals
- ❖ Prairie dogs and squirrels are the carriers in the USA in the Four Corners region
- ❖ Rats are the carrier in urban outbreaks
- ❖ Plague is contracted from flea bites, contamination of open wounds or rarely through human to human respiratory spread











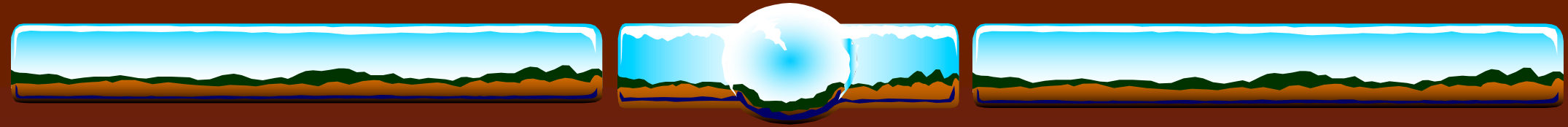


# Plague

- ❖ Dogs are essentially asymptotically infected.
  - ❖ Exception to the rule: Colorado June 2014: Dog to Human transmission-  
- <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6416a1.htm>
- ❖ Cats almost always die from plague
  - ❖ Numerous case reports, especially in NM of Cat to Human transmission of pneumonic plague









# Plague

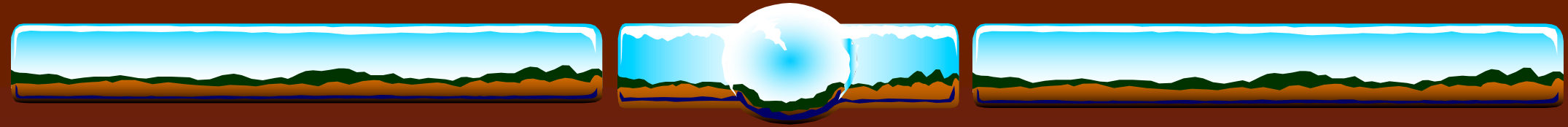
## Clinical manifestations

### ❖ Bubonic Plague

- ❖ Seen in summer months
- ❖ Incubation period is 2-8 days
- ❖ extremely tender, non fluctuant lymph node seen proximal to site of flea bite
- ❖ Skin is red, shiny and edematous











# Plague

## Clinical manifestations (continued)

### ❖ Septicemic Plague

- ❖ fever, N + V, diarrhea, abdominal pain
- ❖ blood cultures always positive
- ❖ High mortality rate

### ❖ Pneumonic Plague

- ❖ bilateral interstitial infiltrates
- ❖ Secondary meningitis, ophthalmitis, arthritis seen





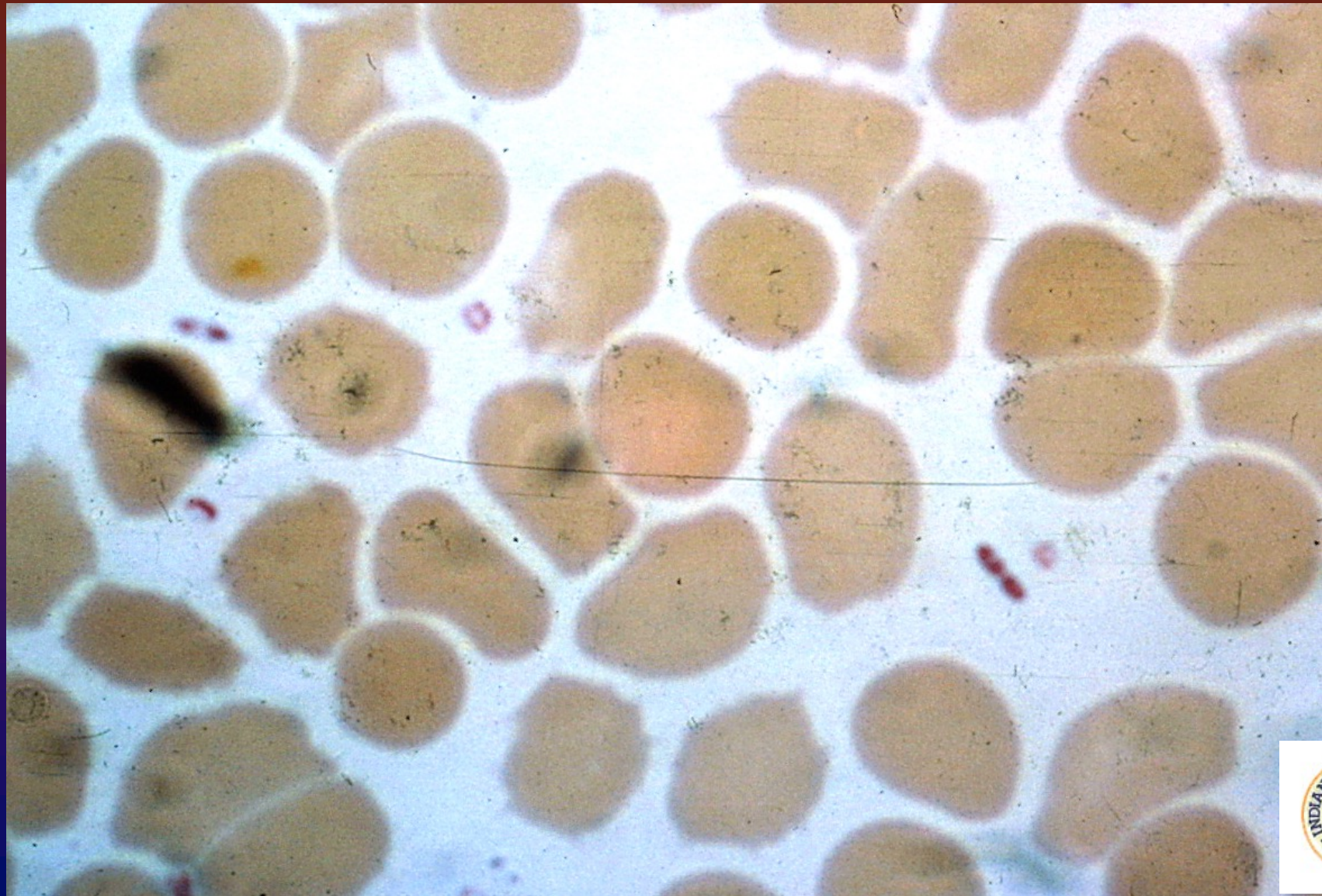
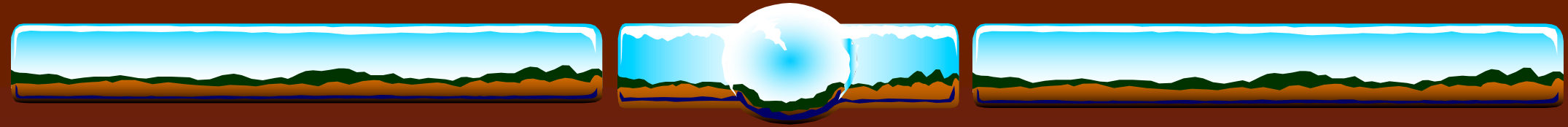
# Plague Diagnosis

## ❖ Aspiration

- ❖ inject 1 cc of saline into node and aspirate
- ❖ Gram stain shows GNR, Geimsa/Wright shows safety pin stained rod
- ❖ Fluorescent antibody stain done at CDC Fort Collins lab
- ❖ Culture the aspirate and blood on routine media









# Plague Therapy

- ❖ Ciprofloxacin is a first choice agent now
- ❖ Gentamicin 5 mg/kg/24h is also used for severe plague
- ❖ Chloramphenicol is active for meningitis, arthritis and shock 15 mg/kg q 6h
- ❖ Doxycycline 100 mg po bid can used for milder cases



# Plague Clinical Pearls

- ❖ Toxic patients with swollen nodes may have plague
- ❖ Consider plague in patients with undifferentiated fever
- ❖ Treat with gentamicin, ciprofloxacin or doxycycline



# References

- ❖ Crook L, Tempest B; Plague: a clinical review of 27 cases; Arch Intern Med. 1992;152(6):1253-1256.  
doi:10.1001/archinte.1992.00400180107017
- ❖ CDC Plague resources for clinicians:  
<https://www.cdc.gov/plague/healthcare/clinicians.html>
- ❖ CDC antimicrobial treatment and prophylaxis:  
[https://www.cdc.gov/mmwr/volumes/70/rr/rr7003a1.htm?s\\_cid=rr7003a1\\_w](https://www.cdc.gov/mmwr/volumes/70/rr/rr7003a1.htm?s_cid=rr7003a1_w)





# Case History

- ❖ A 78 year old female is seen for a bite on the left hand by the family cat which likes to eat road kill. The patient has a draining ulcer on the dorsum of the hand over the fourth metatarsal head. She is treated with Unasyn and discharged home the next day. The patient is subsequently seen elsewhere with persistent drainage and is referred to a tertiary care center. There is a hand ulceration with pus. The pus Gram Stain shows small pleomorphic GNRs.





# Differential Diagnosis

- ❖ MRSA/MSSA
- ❖ *Pasteurella multocida*
- ❖ Necrotizing Fasciitis/Meleney's Gangrene
- ❖ Pyoderma Gangrenosum
- ❖ Tularemia





# Tularemia

- ❖ Caused by Franciscella tularensis, another pleomorphic GNR
- ❖ Carried by rabbits, hares and hard ticks
- ❖ Acquired by
  - ❖ tick bite
  - ❖ cleaning infected animals
  - ❖ animal bites
  - ❖ autoinnoculation





# Tularemia

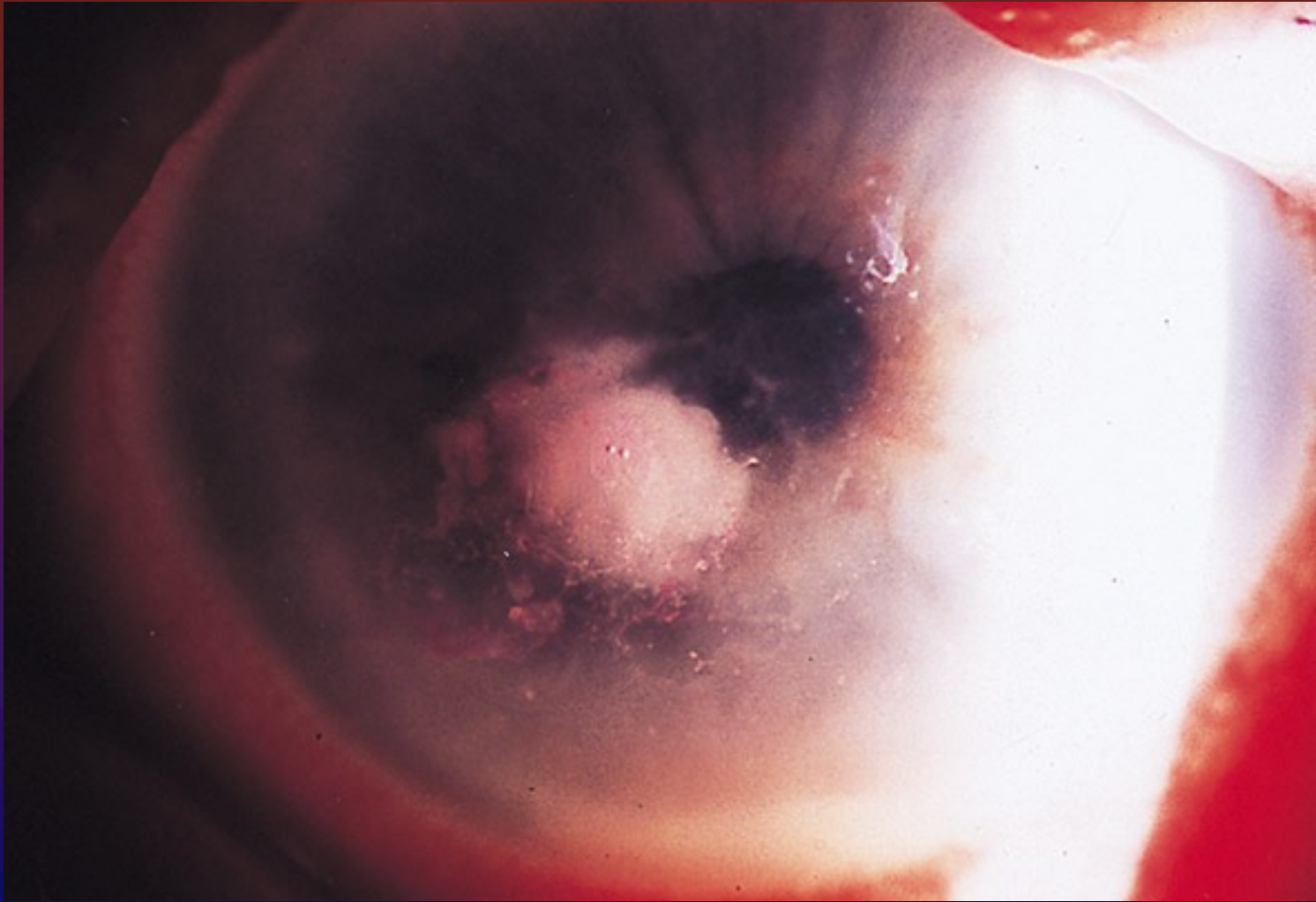
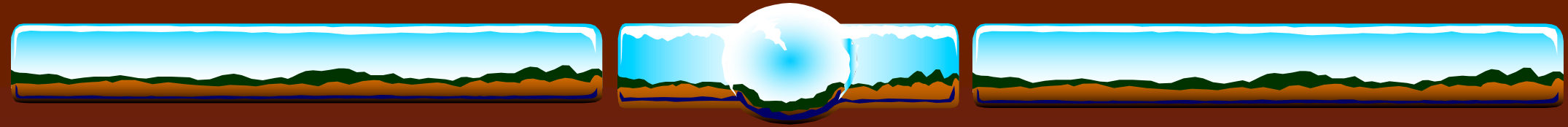
## ❖ Syndromes:

- ❖ Ulceroglandular: ulcer with proximal node
- ❖ Oculoglandular: preauricular node with conjunctivitis
- ❖ Oropharyngeal: exudative pharyngitis
- ❖ Pleuropulmonary: pneumonia with mediastinal nodes
- ❖ Typhoidal: fever and malaise











# Tularemia Treatment

## ❖ Treatment Regimens:

- ❖ Gentamicin 5 mg/kg IV daily for 10-14 days are preferred traditionally
- ❖ Ciprofloxacin and doxycycline are also highly active





# Tularemia Clinical Pearls

- ❖ Think:

- ❖ Ticks

- ❖ Rabbits

- ❖ Grass mowing

- ❖ Bioterrorism

- ❖ Treat like plague





# References

❖ CDC guidance:

<https://www.cdc.gov/tularemia/clinicians/index.html>



# Case Presentation

- ❖ A 30 year old woman comes to the ED complaining of hives and dizziness during sexual intercourse.
- ❖ The patient had a history of developing hives after eating at a Chinese restaurant in a reservation border-town. She went immediately to the emergency room and was found to be in anaphylactic shock. She was resuscitated and did well. Now she only gets hives with intercourse.





## Case Presentation

- ❖ On physical exam the patient appears well. Her skin exam is notable for the absence of hives. She is moderately obese and has a normal abdominal and pelvic exam. Routine laboratory tests are notable only for a WBC of 10 with 9% eosinophils.





# Case Presentation

- ❖ A CT scan of the abdomen and pelvis shows a 4 cm cystic mass adjacent to the uterus with normal adnexae. There is a second cystic lesion in the liver parenchyma. The hepatic lesion is inhomogeneous but appears fluid filled.



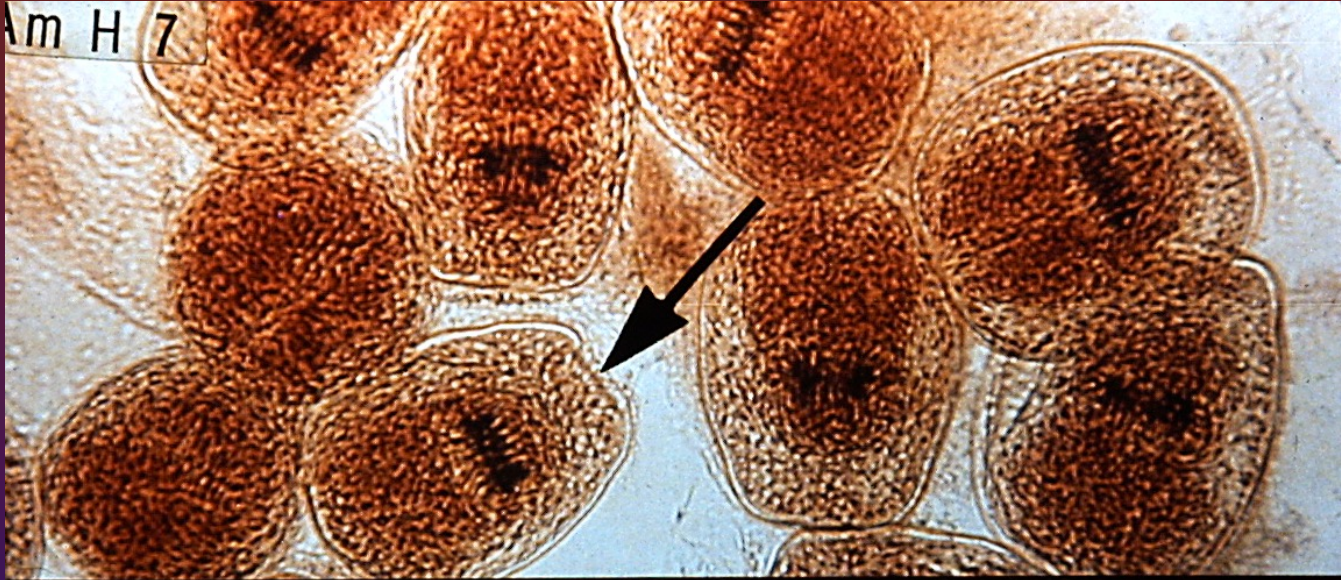


# Echinococcosis

## ❖ Etiology:

- ❖ Caused on Navajo by dog tapeworm *Echinococcus granulosus*.
  - ❖ Cestode parasite: tapeworm
  - ❖ Larval metacestodes cause the human disease
  - ❖ Causes Cystic echinococcosis
- ❖ Caused among Alaskan Natives by wolf tapeworm *E. multilocularis*
  - ❖ Causes alveolar echinococcosis







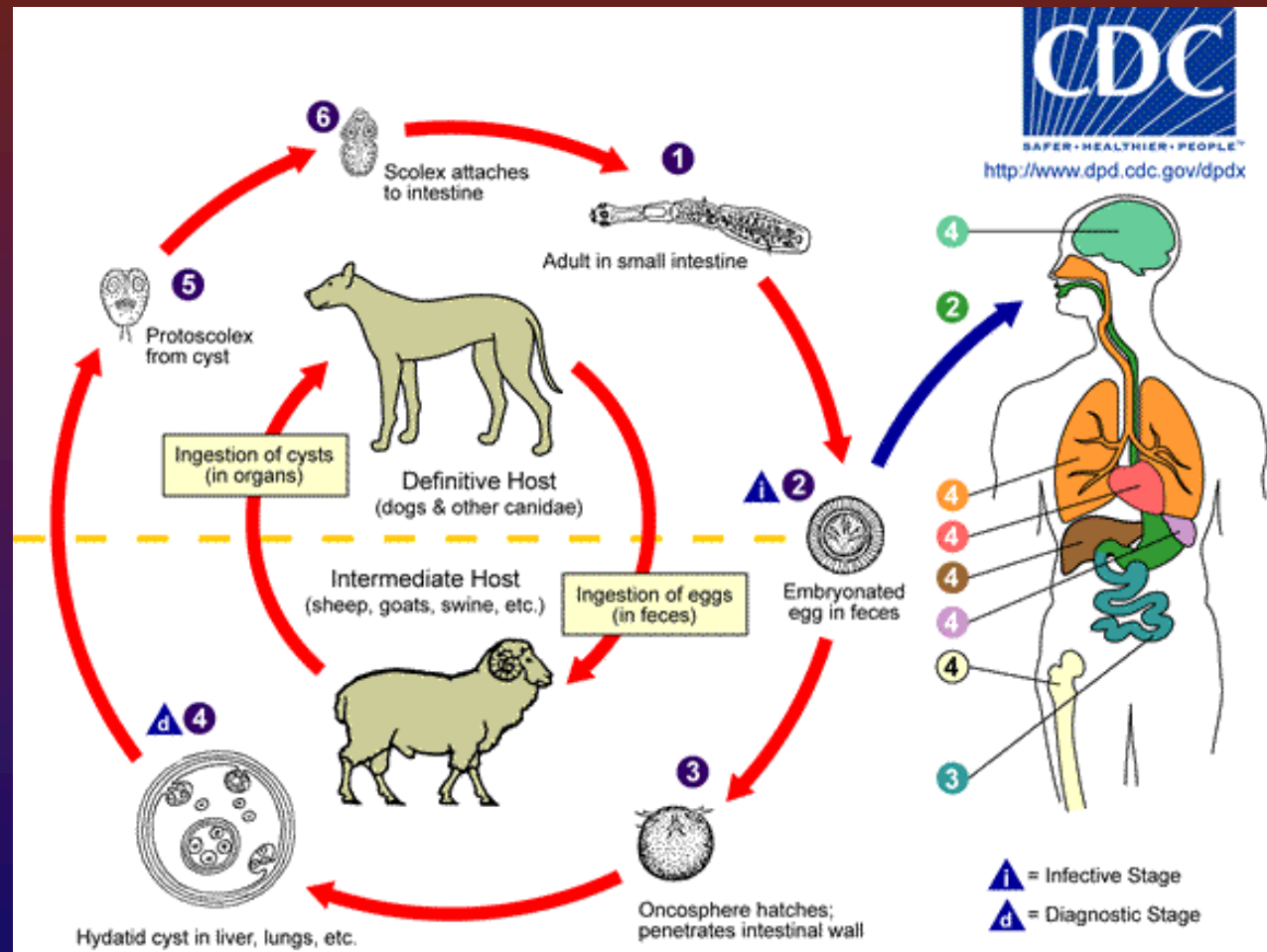
# Echinococcosis

## ❖ Epidemiology

- ❖ Dogs and wolves carry the adult tapeworm in their gut
- ❖ Sheep serve as the intermediate host carrying larvae in cysts
- ❖ Humans serve as an accidental intermediate host











# Echinococcosis-Life Cycle

- ❖ **Adult tapeworms** in dogs lay eggs
- ❖ **Humans ingest eggs** in food contaminated by dog feces.
- ❖ **Oncospheres** “hatch,” cross into the blood and are carried to the liver, lung and brain
- ❖ **Large cysts** form with smaller daughter cysts inside.



# The Hydatid cyst

- ❖ 80% involve a single organ

  - ❖ 80% liver; 20% lung

- ❖ **Cyst Structure:**

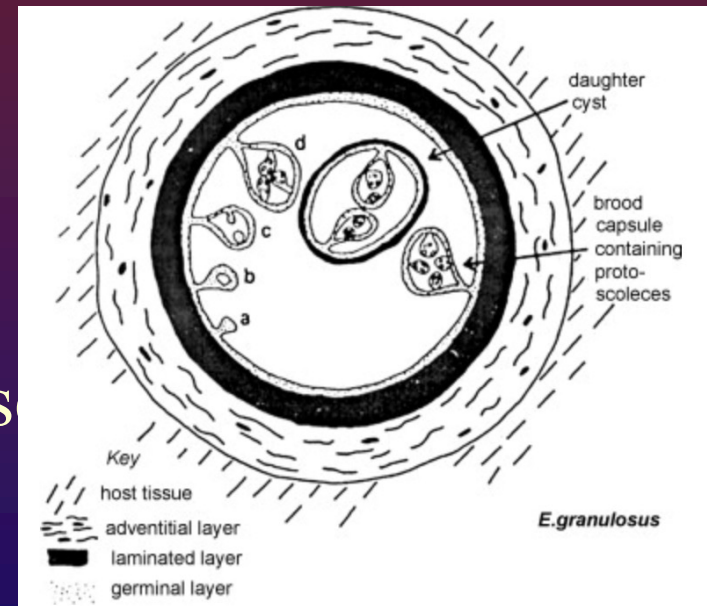
  - ❖ **Adventitial** layer: host derived response

  - ❖ Acellular **laminated** layer

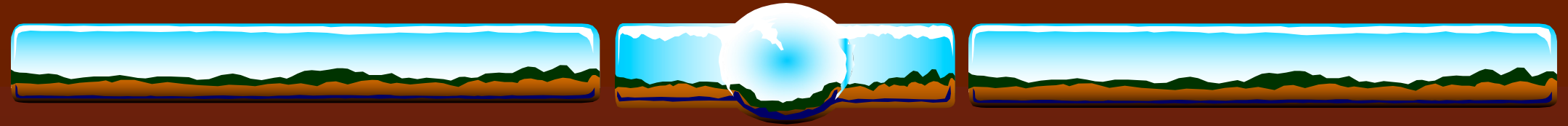
  - ❖ **Germinal** layer produces

    - ❖ Brood Capsules

    - ❖ Daughter cysts



Ernst, A. Tropica, 2010. <https://www.sciencedirect.com/science/article/pii/S0001706X09003581?via%3Dihub>



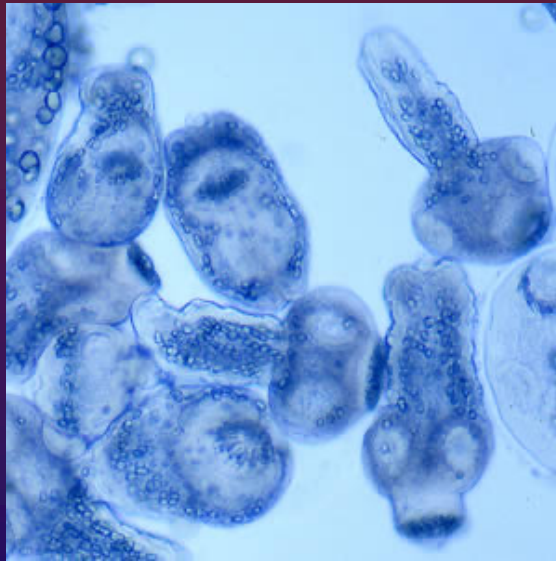


JV Iralu, JH Maguire, Sem Resp Infect, 1991  
<https://pubmed.ncbi.nlm.nih.gov/1810002/>





*Echinococcus granulosus* protoscolices  
liberated from a hydatid cyst

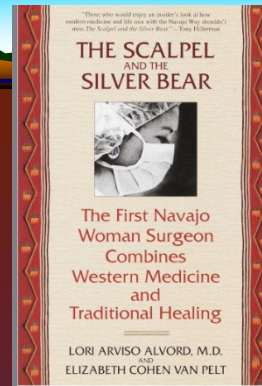


<https://www.cdc.gov/dpdx/echinococcosis/index.html>





# Echinococcosis- Clinical Manifestations



- ❖ Largely asymptomatic until they cause mass effect (grow 1 cm per year)
- ❖ Can cause anaphylaxis, urticaria, eosinophilia or bronchospasm with rupture or small leaks.
- ❖ Can rupture into the bronchi, biliary tree and intestine causing dissemination.



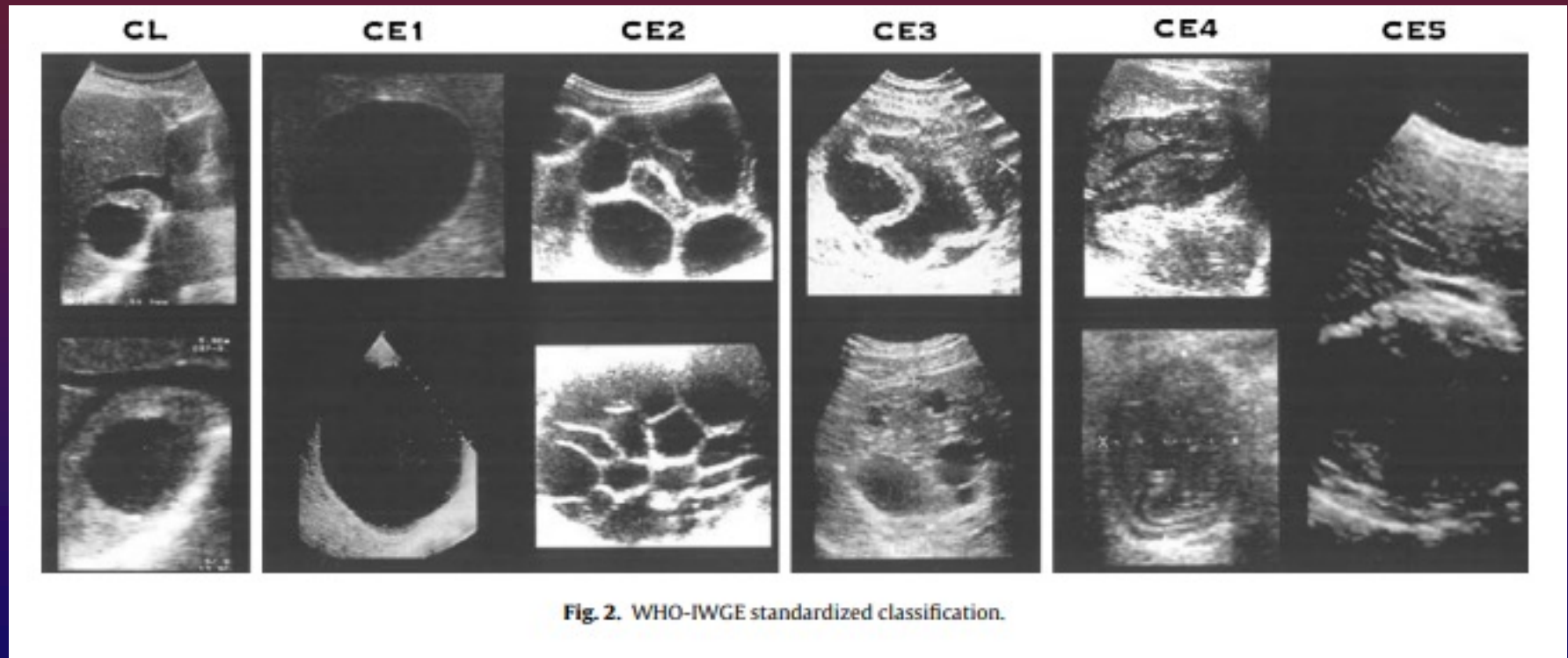
# Echinococcosis-Diagnosis

- ❖ **Radiology:** Large thin or thick walled cysts with wall calcification and daughter cysts on CT are pathognomonic.
  - ❖ Double Line Sign, honeycomb sign, rosette sign, Water lilly sign
  - ❖ Hydatid sand shifts on Ultrasound with position shift
- ❖ **Serology** is helpful but a negative test does not rule out Echinococcosis
  - ❖ **Dot EIA**
    - ❖ 85-95% positive with liver cysts
    - ❖ 65% positive with lung cysts
  - ❖ **Immunoblot** assay





# WHO stages





# WHO Staging

World Health Organization classification of cystic echinococcosis and treatment stratified by cyst stage

WHO stage	Description	Stage	Size	Preferred treatment	Alternate treatment
CE1	Unilocular anechoic cystic lesion with double line sign	Active	<5 cm	Albendazole alone	PAIR
			>5 cm	Albendazole + PAIR	PAIR
CE2	Multiseptated, "rosette-like" "honeycomb" cyst	Active	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE3a	Cyst with detached membranes (water-lily sign)	Transitional	<5 cm	Albendazole alone	PAIR
			>5 cm	Albendazole + PAIR	PAIR
CE3b	Cyst with daughter cysts in solid matrix	Transitional	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE4	Cyst with heterogeneous hypoechoic/hyperechoic contents; no daughter cysts	Inactive	Any	Observation	-
CE5	Solid plus calcified wall	Inactive	Any	Observation	-



# Echinococcosis- Treatment

- ❖ Resection is curative
  - ❖ Preop  
Albendazole (1 day before, 4 weeks after)
  - ❖ 20% hypertonic saline is injected into the cyst before opening
  - ❖ Best for complicated superficial cysts that might rupture, or compression or invading biliary tree
- ❖ “PAIR” for cysts > 5cm (plus drug therapy)
  - ❖ puncture, aspirate, inject 20% hypertonic saline, reaspirate after 15 minutes
  - ❖ **Modified catheter**: large cutting needle to aspirate the entire cyst
- ❖ Drugs for cysts < 5cm as monotherapy
  - ❖ Albendazole 400 mg po bid X 28 days for 3 cycles (follow LFTs and CBC, hair)
  - ❖ Praziquantel for cyst rupture to kill protoscolices





# Post Treatment Follow Up

- ❖ US post-treatment every 3-6 months until stable then annually
- ❖ Continue to scan for 3-5 years



# Echinococcosis clinical pearls

- ❖ Look for a slowly growing cystic mass
- ❖ Look for eosinophils on the differential
- ❖ Treat with Albendazole, PAIR and Surgery



## References

- ❖ **Bruneti et al. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans** *Acta Trop.* 2010 Apr;114(1):1-16.
  - ❖ doi: 10.1016/j.actatropica.2009.11.001.Epub 2009 Nov 30
- ❖ **Higueta et al. Cystic Echinococcosis.** *J Clin Microbiol.* 2016 Mar; 54(3): 518–523.



## Case Presentation

- ❖ A 65-year-old female sheep herder comes from sheep camp to the ED with drenching sweats, myalgias, nausea and vomiting of 3 weeks duration. PE shows a toxic appearance with clear lungs and minimal RUQ tenderness. Labs are notable for a platelet count of 125K, AST 120, ALT 145, Alk Phos 197 and Bili 1.8, UA and CXR are normal.





# Differential Diagnosis

- ❖ RMSF
- ❖ Relapsing Fever- *Borrelia hermsii*
- ❖ Plague
- ❖ Hantavirus
- ❖ Q-Fever



## Q-Fever basics

- ❖ *Coxiella burnetii* is a pleomorphic gram-negative coccobacillus related to *Legionella*
- ❖ Described in 1935 in Australia
  - ❖ The “Q” stool for “Query”
- ❖ Carried by ungulates such as sheep, goats and cows plus horses, dogs, pigs, camels, pigeons, ducks, geese & turkeys



# Pathophysiology

- ❖ Humans inhale aerosolized placental/amniotic fluids at the time of livestock parturition
- ❖ Incubation period is 20 days
- ❖ Bacteria cause a pneumonia followed by bacteremia with dissemination
- ❖ Endocarditis is the complication of concern



# Clinical Presentation

- ❖ Acute febrile illness 1-2 weeks duration is most common
- ❖ Atypical pneumonia
- ❖ Severe headache, lethargy, chills, myalgias, N/V, diarrhea
- ❖ Acute hepatitis
- ❖ Chronic Q fever:
  - ❖ Endocarditis involving valves or preexisting aneurysm
  - ❖ Granulomatous hepatitis
  - ❖ Osteomyelitis



# Diagnosis

## ❖ Labs

- ❖ Leukocytosis or leukopenia
- ❖ Thrombocytopenia or thrombocytosis
- ❖ Elevated LFTs except normal bilirubin
- ❖ CSF pleocytosis

## ❖ CXR: Pulmonary infiltrates

## ❖ Serologies:

- ❖ Phase II Ab is higher in acute Q Fever
- ❖ Phase I Ab  $> 1:1024$  is the marker for chronic q fever



# Treatment of Q Fever

- ❖ Doxycycline 100 mg po bid for acute Q fever x 14 days
- ❖ TMP-sulfa or moxifloxacin are alternates
- ❖ Doxycycline/Hydroxychloroquine are used for chronic Q fever





# Q Fever Clinical Pearls

- ❖ Think Q fever with
  - ❖ atypical pneumonia and
  - ❖ livestock exposure, especially in lambing season
- ❖ Send a Q-Fever antibody panel
- ❖ Treat with Doxycycline for 2 weeks



# References

❖ CDC guide to treatment:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6203a1.htm>



# Case Presentation

- ❖ A 72 year old woman comes in to the emergency department complaining of severe headache, myalgias and fever. Her physical examination is notable for fever of 104 degrees F, clear lungs, no murmur and a benign abdomen. Routine laboratories are notable only for a platelet count of 121K.





# Case Presentation

- ❖ The manual differential you ordered shows no immunoblasts but is full of spirochetes. On further questioning you find that the patient is a medicine woman who spent last weekend performing a puberty ceremony for her niece. Eventually 39 members of her family sought care at multiple hospitals in the Four Corners area for a similar febrile illness.





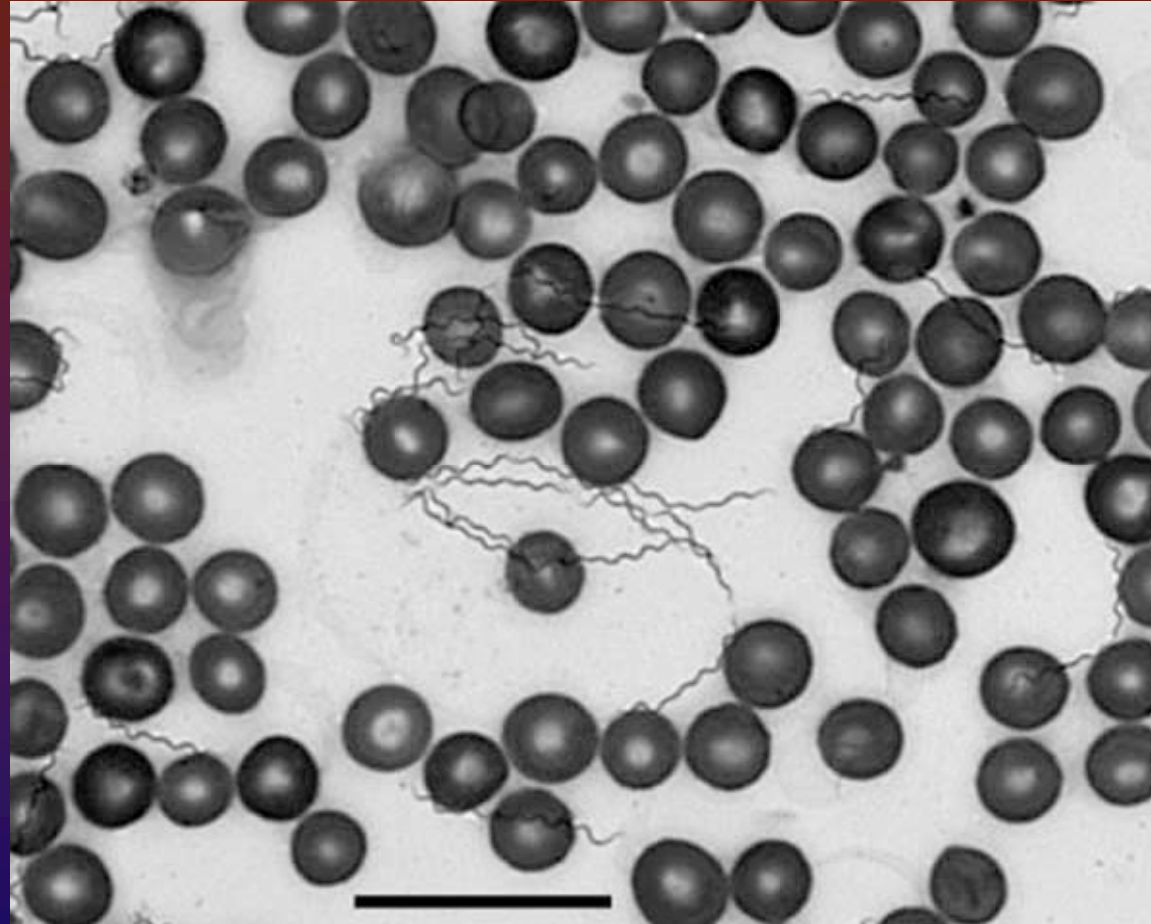
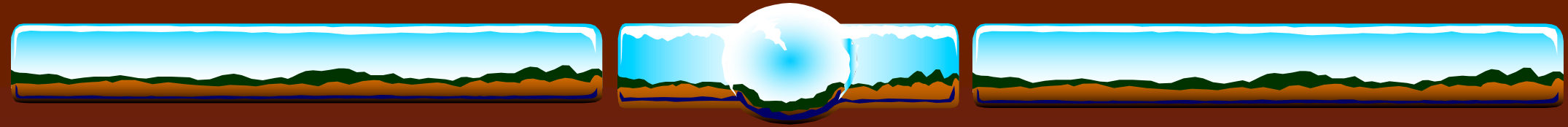
# Tickborne Relapsing Fever

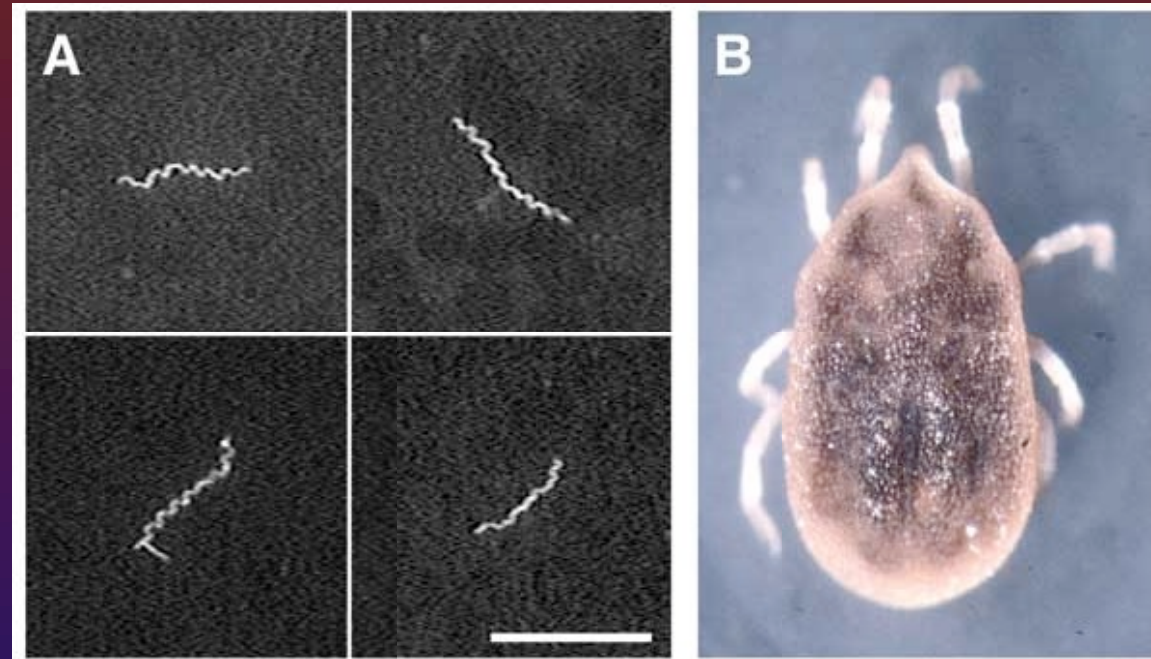
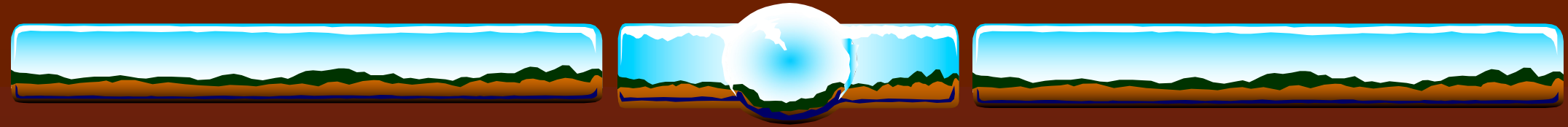
## Etiology

- ❖ Caused by the spirochete *Borrelia hermsii* or *B. turicatae* in the American Southwest.
- ❖ Carried by chipmunks and small rodents and transmitted to humans via bite of the *Ornithodoros* soft tick.
- ❖ Lives at altitudes  $> 1,500$  feet in caves and rural cabins with a moist microenvironment.











# Tickborne Relapsing Fever

## Clinical Syndrome

- ❖ Tick feeds < 1 hour
- ❖ Incubation period 7 days [2-18]
- ❖ Symptoms:
  - ❖ Recurrent fever every 3 days (Antigenic Variation)
  - ❖ headache
  - ❖ rigors
  - ❖ myalgia/arthralgia
  - ❖ N & V





# Tickborne Relapsing Fever

## ❖ Diagnosis

- ❖ Peripheral blood smear shows spirochetes
- ❖ Blood Cultures positive for Borrelia
- ❖ Acute and Convalescent titers confirm Dx.

## ❖ Treatment (Beware Jarisch-Herxheimer)

- ❖ Penicillins
- ❖ Doxycycline





# Tickborne Relapsing Fever Prevention

- ❖ Avoid abandoned cabins
- ❖ Wear DEET
- ❖ Rodent proof buildings
- ❖ Fumigation with Pyrethrins





# Borrelia Clinical Pearls

## ❖ Think

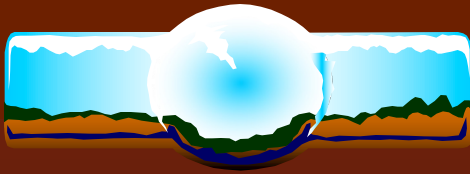
- ❖ Isolated cabins with little rodents
- ❖ Innocuous tick bites followed by fever and headache
- ❖ Look for “worms” on the blood smear
- ❖ Treat with PCN or doxycycline





# References

- ❖ CDC guidance: <https://www.cdc.gov/relapsing-fever/clinicians/index.html>
- ❖ Case report of the event:  
<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5234a1.htm>





## Case presentation

- ❖ A 31 year old man presents to the walk-in clinic with a chief complaint of diarrhea, abdominal cramps and back pain. On exam he has a fever of 102 degrees, a moderately toxic appearance and a mildly tender abdomen. Laboratory data are as follows: WBC 12K, Hct 50%, Platelets 121, ALT 56, Alk Phos 121, Bili 1.3, Glucose 147. A CXR is normal as is the urinalysis.





# Differential Diagnosis

- ❖ Septicemic plague
- ❖ Tularemia
- ❖ Rocky Mountain spotted fever
- ❖ Primary pneumococcal bacteremia
- ❖ Group A Strep Toxic shock syndrome
- ❖ Hantavirus pulmonary syndrome prodrome
- ❖ Cardiogenic Pulmonary Edema





# Hantavirus Pulmonary Syndrome

## ❖ History

- ❖ First recognized at Gallup Indian Medical Center by Bruce Tempest and Larry Crook in April 1993.
- ❖ Earliest American case retrospectively diagnosed by serology was July 1959
- ❖ Confirmed by immuno-histochemical staining of post-mortem tissue from a case from 1978

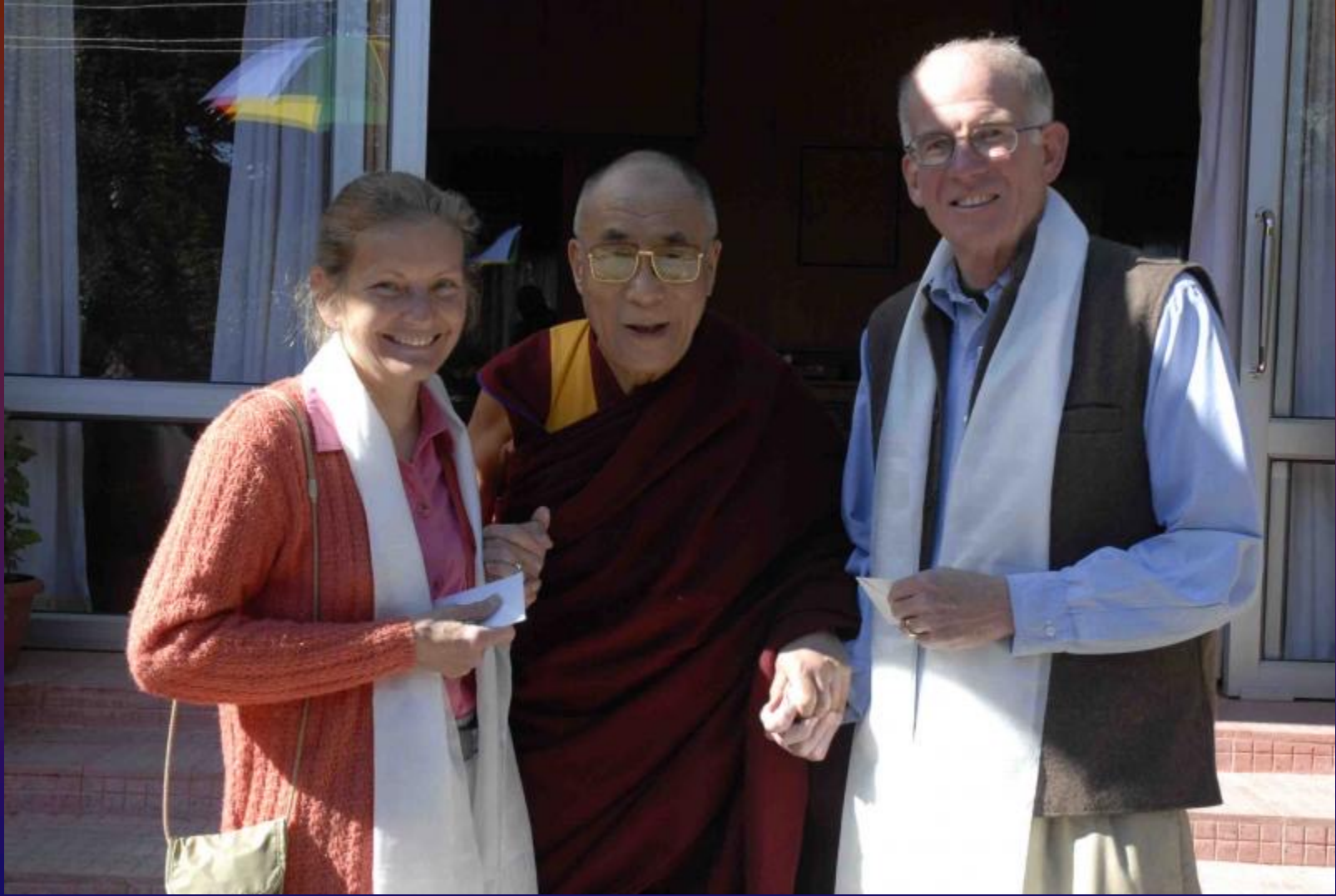






*Bruce Tempest*







# Hantavirus Pulmonary Syndrome Ecology

## ❖ US Vectors

### ❖ Sin Nombre Virus:

❖ Deer Mouse

(Peromyscus maniculatus)

### ❖ Black Creek Canal Virus (Dade Co., FL)

❖ Cotton rat

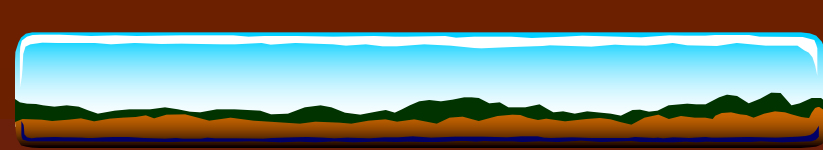
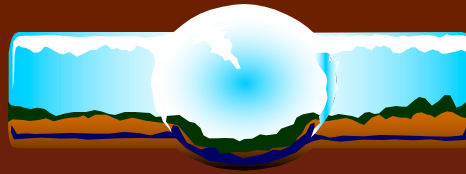
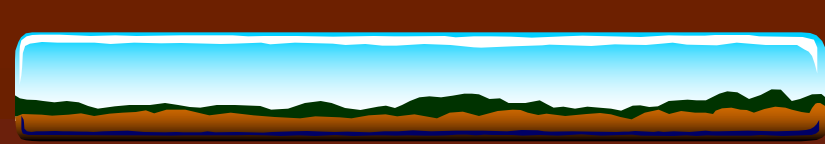
(Sigmodon Hispidus)

### ❖ New York-1

❖ White Footed Mouse

(Peromyscus leucopus)







# New World Hantaviruses





# Hantavirus Pulmonary Syndrome

## ❖ Virology

- ❖ Bunyavirus family
- ❖ negative sensed ss RNA virus
- ❖ All other Bunyaviruses are arthropod-borne

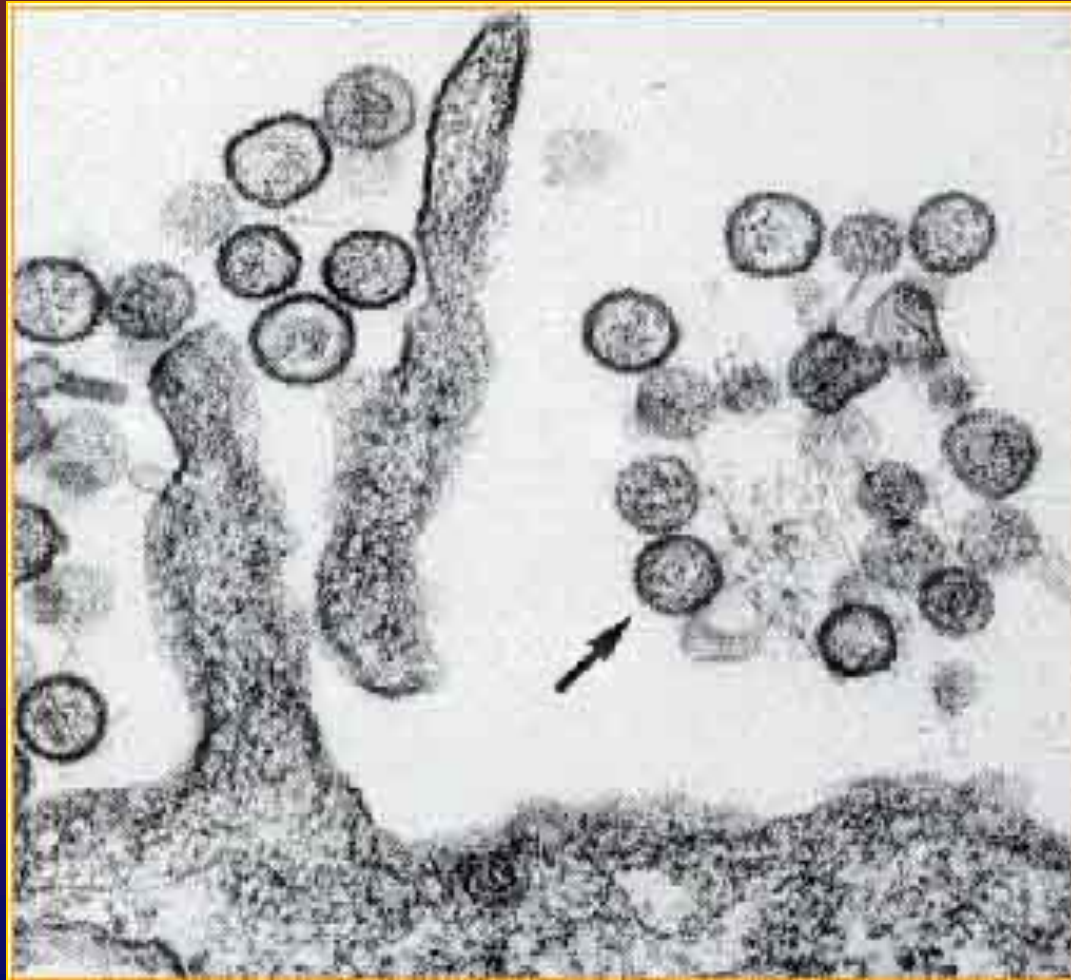
## ❖ Structure

### ❖ Three RNA segments

- |              |                         |
|--------------|-------------------------|
| ❖ S (small)  | Nucleocapsid            |
| ❖ M (medium) | Envelope glycoproteins  |
| ❖ L (large)  | Transcriptase/Replicase |



# Sin Nombre Virus Characteristics







# HPS Clinical Presentation

## ❖ Febrile Prodrome Phase

### ❖ Most Frequent:

❖ fever, chills, myalgia

### ❖ Frequent:

❖ headache, nausea & vomiting, abdominal pain, diarrhea, cough, malaise

### ❖ Other:

❖ SOB, dizziness, arthralgia, back/chest pain, sweats





# HPS Clinical Presentation

## ❖ Not likely to be Hantavirus Prodrome if:

- ❖ rash
- ❖ conjunctival or other hemorrhage
- ❖ throat or conjunctival erythema
- ❖ petechiae
- ❖ peripheral or periorbital edema



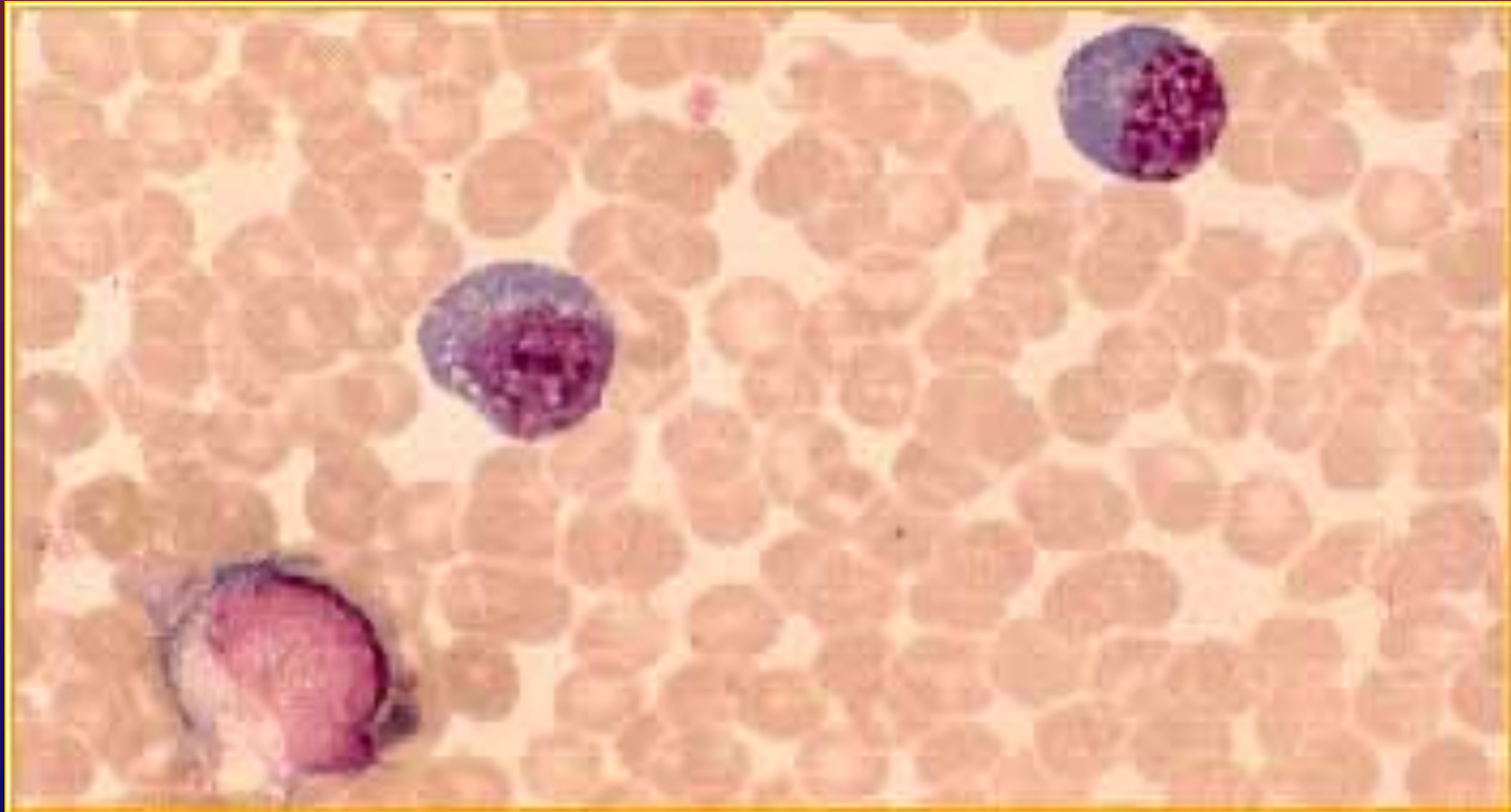
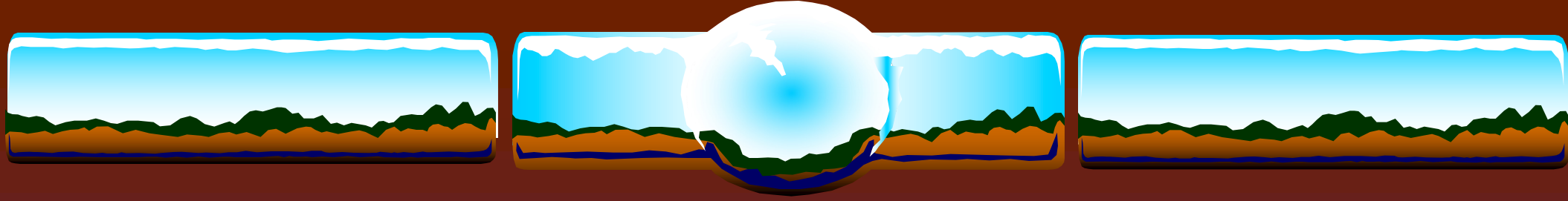


# HPS Clinical Presentation

## ❖ Laboratory Evaluation

- ❖ **Thrombocytopenia is the most important marker for HPS**
- ❖ Falling albumin and rising hematocrit mark fluid shifts from endovascular space to lung
- ❖ Bands, atypical lymphocytes and immunoblasts are seen as the disease progresses.







# References

- ❖ Four Corners Hantavirus video for providers:  
<https://www.youtube.com/watch?v=ukkVLgpAKnc>

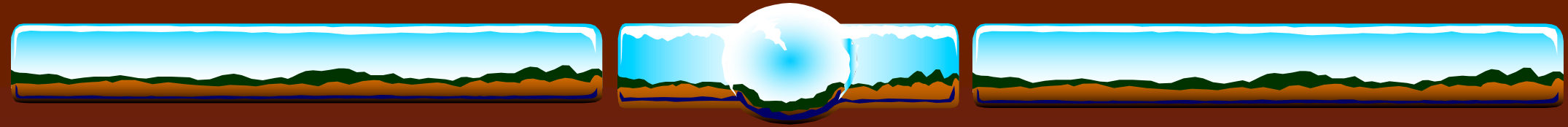


# Koster-Foucar Smear Criteria

- ❖ Hemoconcentration ( $> 50\%$  HCT males,  $48\%$  females)
- ❖ Thrombocytopenia  $< 150\text{K}$
- ❖ Leukocytosis with left shift
- ❖ Absence of toxic granules
- ❖ Immunoblasts make up  $> 10\%$  of lymphocytes

4 out of 5 met: 96% Sensitive, 99% Specific







# HPS Clinical Presentation

## ❖ Pulmonary Syndrome Phase

- ❖ hypotension and pulmonary edema and effusion
- ❖ severe pump failure is the terminal event
  - ❖ *(low cardiac output with high SVR)*
  - ❖ *lactate > 4mmol/L or CI, 2.2 L/min/mm<sup>2</sup> portend a poor prognosis*
- ❖ **MOSF is rare**





# HPS Clinical Presentation

## ❖ Recovery Phase

- ❖ Polyuric diuresis
- ❖ Rapid improvement is seen
- ❖ Chronic asthenia, myalgia, pulmonary function abnormalities are seen in the survivors.





# HPS Clinical Presentation

## ❖ Diagnosis

- ❖ ELISA for SNV IgM available at CDC
- ❖ IgG ELISA also available for acute and convalescent sera
- ❖ Immunoblot Assay formerly available at UNM Virology Laboratory





# HPS Treatment

- ❖ ICU Care is critical!
  - ❖ NO IV FLUID !!!!!!!!!!!!!
  - ❖ Don't intubate in the field (if you can help it) !!!!!!!
  - ❖ Pressors: Norepinephrine is the best pressor
  - ❖ ECMO
  - ❖ There are no good antivirals





# Hantavirus clinical pearls

- ❖ Think gastroenteritis early, shock with pneumonia later.
- ❖ Look for the low platelet count
- ❖ Call the plane early!