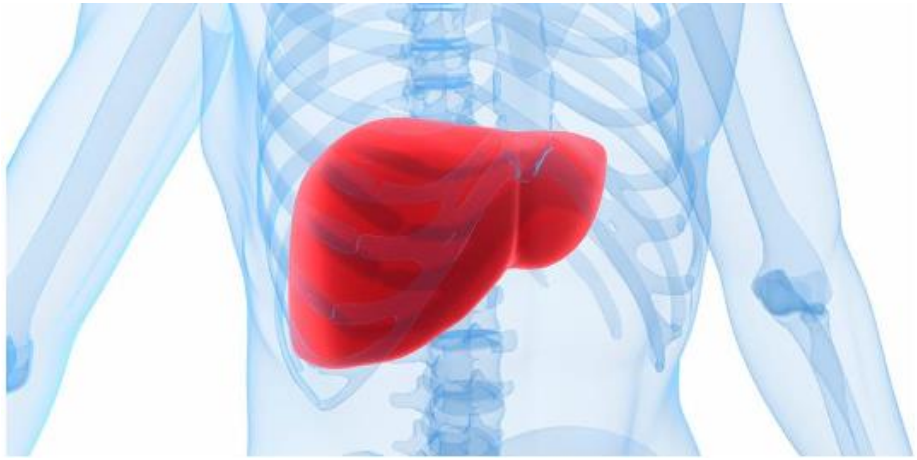
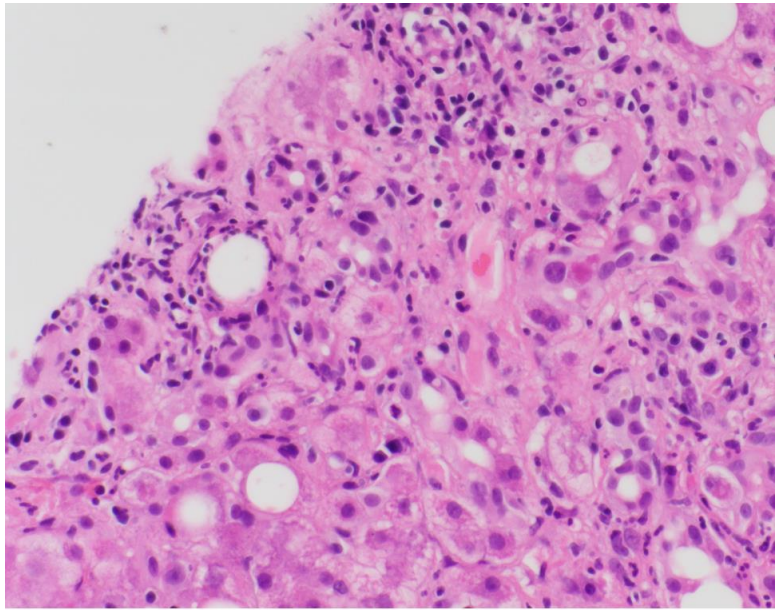
ARUP LABORATORIES

An infectious cause of acute liver injury





Skyler J. Simpson, MD

PGY-4 Pathology Resident

Learning Objectives

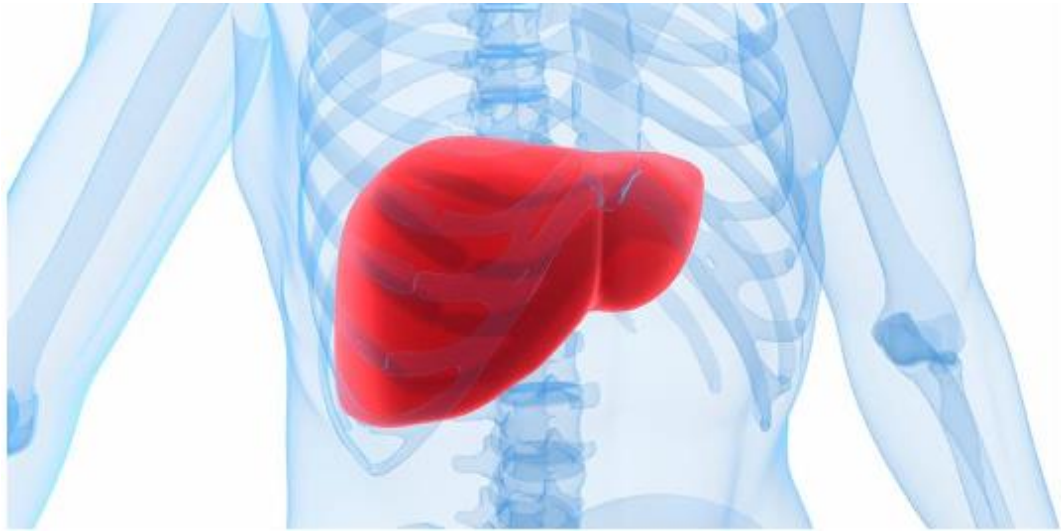
1. Understand the interpretation of serologic testing for Epstein-Barr Virus

2. Describe the basic microbiology and transmission of *Coxiella burnetii*

3. Explain the serologic testing for Q fever and how we differentiate between acute and chronic infections

Outline

- Clinical case presentation
- Review of liver anatomy and function
- Laboratory values
- Epstein-Barr Virus
  - Background and clinical features
  - Laboratory testing
- Liver biopsy results
- Q fever
  - Introduction and epidemiology
  - Transmission and clinical manifestations
  - Microbiology
  - Laboratory testing
  - Treatment
- Summary



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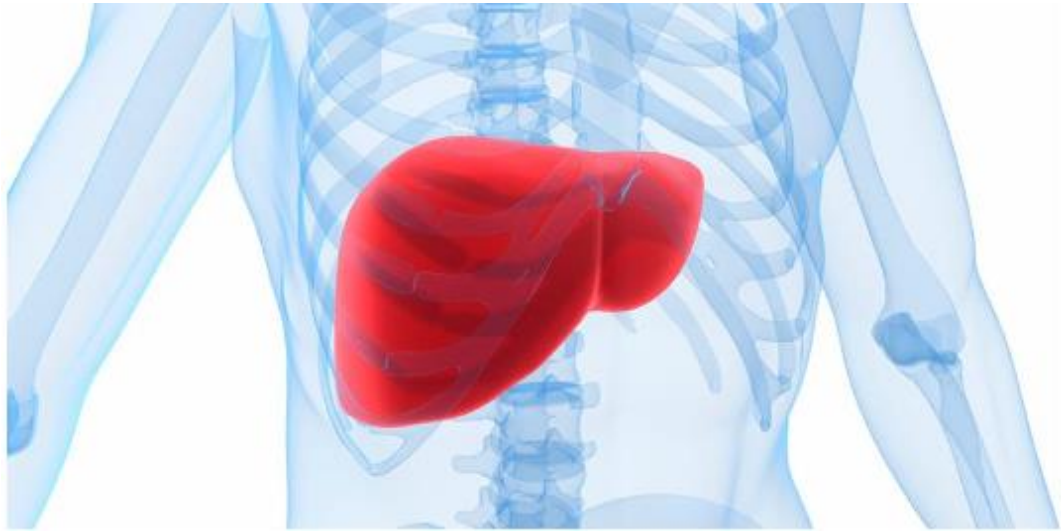

Clinical case presentation

- 59 year-old male with past medical history of alcohol use disorder (drinks 12 beers/day for as long as he can remember) presents to urgent care with recent jaundice, diarrhea, nausea, and mid-abdominal pain.
- Two weeks ago, he quit drinking and was using a new herbal supplement (unknown name) from Mexico to decrease alcohol use.
- He misunderstood the instructions for the medication and took 15 days worth of the drug over the course of 3 days which led to the development of his symptoms.
- Most symptoms resolved after a few days, but the jaundice and abdominal pain persisted

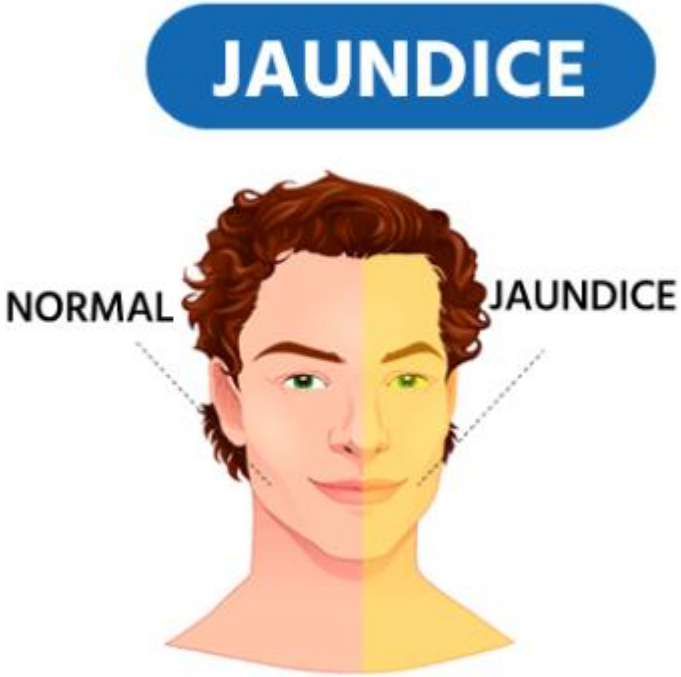

Image from https://www.medicoverhospitals.in/diseases/jaundice

Clinical case presentation

- **Family history:** No significant family history of liver disease
- **Social History:**
  - Never smoker
  - No IV drug use
  - Not vaccinated for viral hepatitis B
  - No travel history outside of the US within the past year
- **Physical Examination**: Patient is jaundiced with scleral icterus, abdominal distension, and tachycardia
- Patient admitted to the hospital for further workup by hepatology

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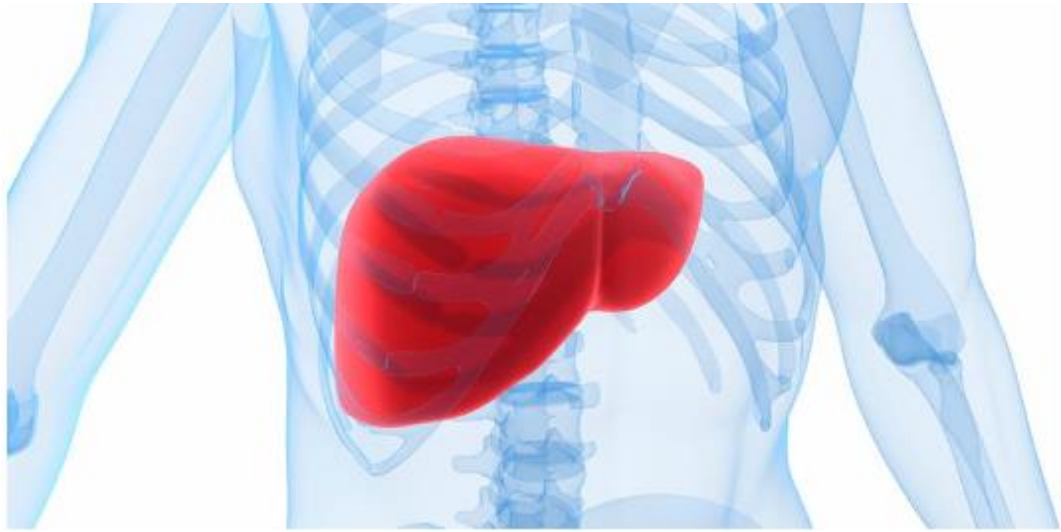


The Liver

- The liver is in the RUQ of the abdominal cavity
- Weight: 1500-1800 grams (3-4 lbs)
- Major functions:
  - Production of bile
  - Protein production (albumin, clotting factors…)
  - Fat soluble vitamin storage/metabolism
  - **Bilirubin metabolism (heme breakdown)**
  - Drug metabolism
  - Cholesterol and glucose metabolism
  - Protein metabolism (ammonia)

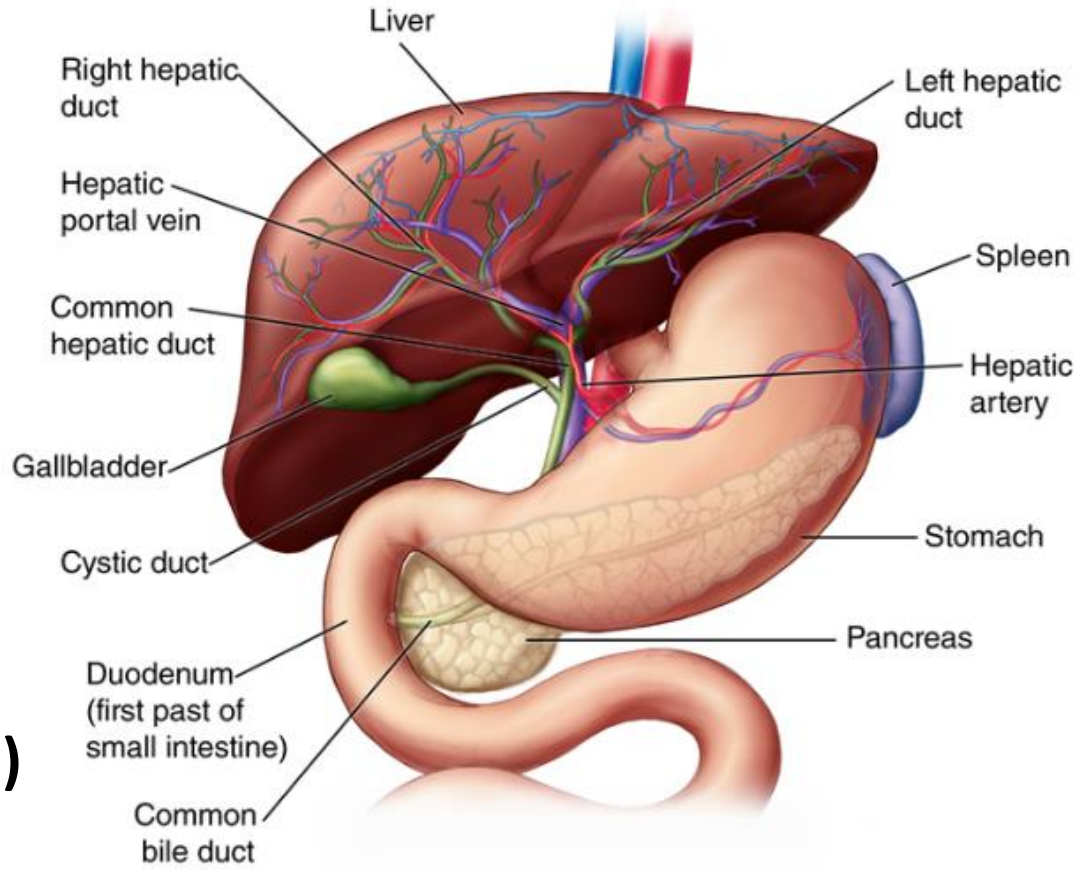


Image from https://www.hopkinsmedicine.org/health/conditions-and-diseases/liver-anatomy-and-functions

[1] https://www.ncbi.nlm.nih.gov/books/NBK535438/

Liver Gross Anatomy Images

Normal liver

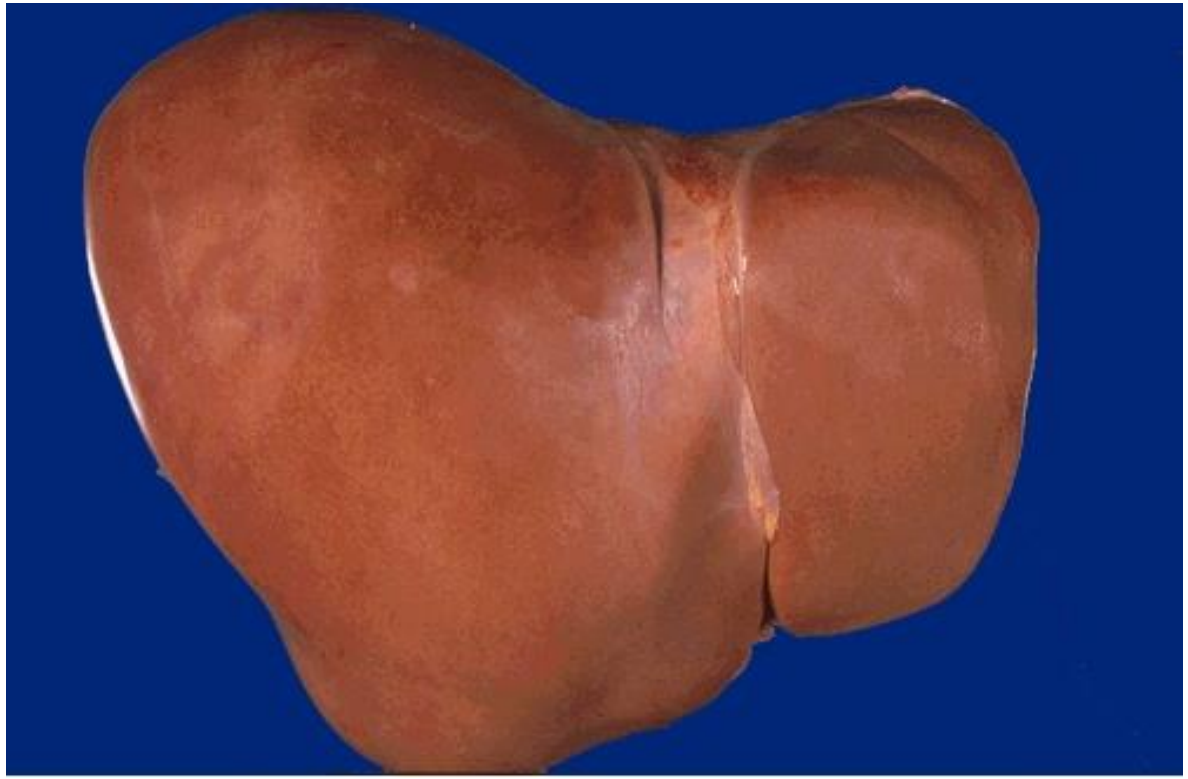
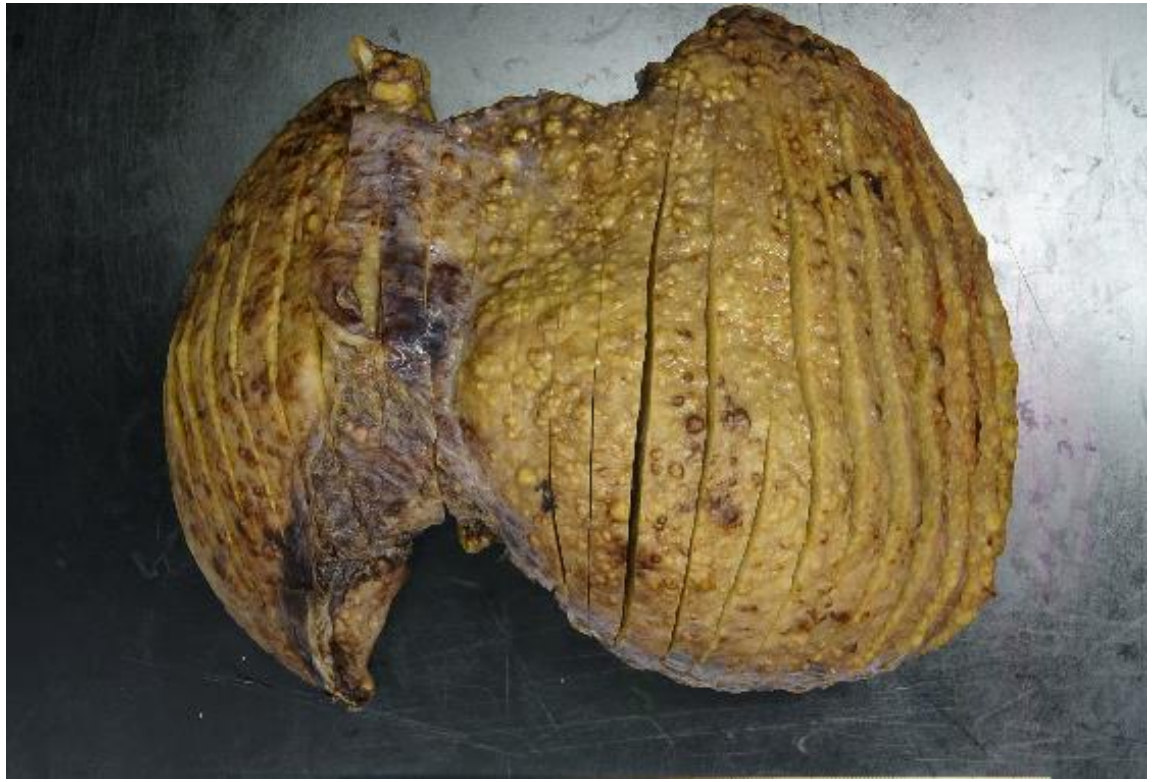


Image from https://webpath.med.utah.edu/LIVEHTML/LIVER002.html

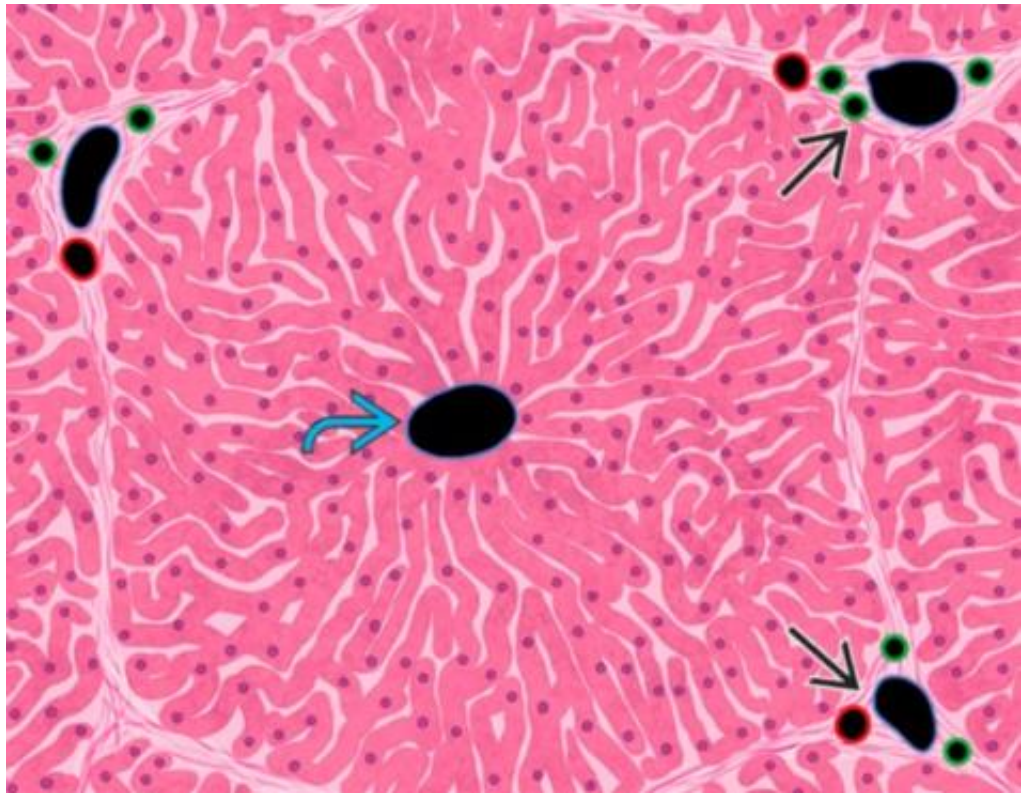
Liver Cirrhosis



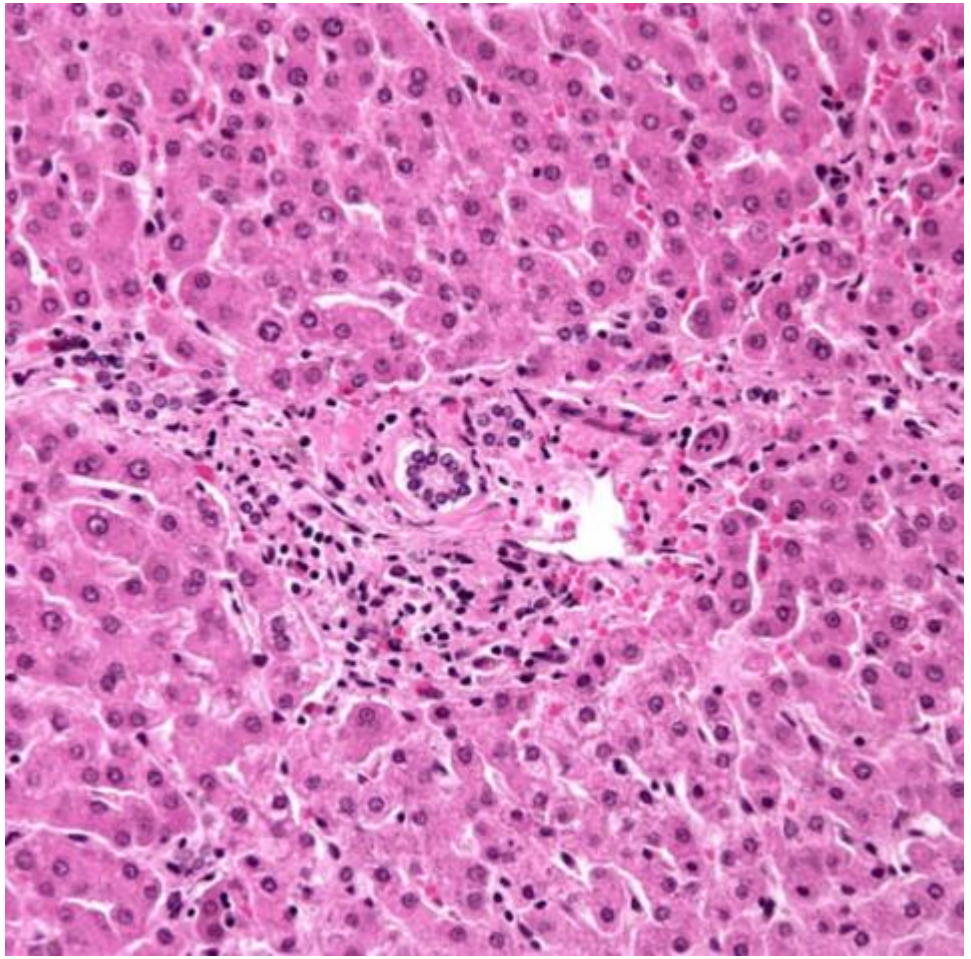
Gross image from a case of liver cirrhosis

Liver Microscopic Images

Liver architecture diagram



Normal Liver Histology



Images from Expertpath.com

Differential diagnosis for liver injury

- Autoimmune
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Autoimmune hepatitis
- Genetic
  - Wilson disease
  - Alpha-1-antitrypsin deficiency
  - Hemochromatosis
  - Crigler-Najjar syndrome
- Viral Infection
  - Hepatitis A, B, C, or D
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Herpes Simplex virus (HSV)
- Nonalcoholic liver disease
  - Congestive heart failure
  - Biliary disease
  - Nonalcoholic steatohepatitis
- **Toxins**
  - **Alcohol**
  - Aflatoxin
  - Acetaminophen
  - **Other drugs**
- Hematologic syndromes
  - HELLP
  - Ischemia
  - Budd-Chiari syndrome

[2]Genzen JR, Slev, PR. Liver disease evaluation. ARUP consult. https://arupconsult.com/content/liver-disease-evaluation

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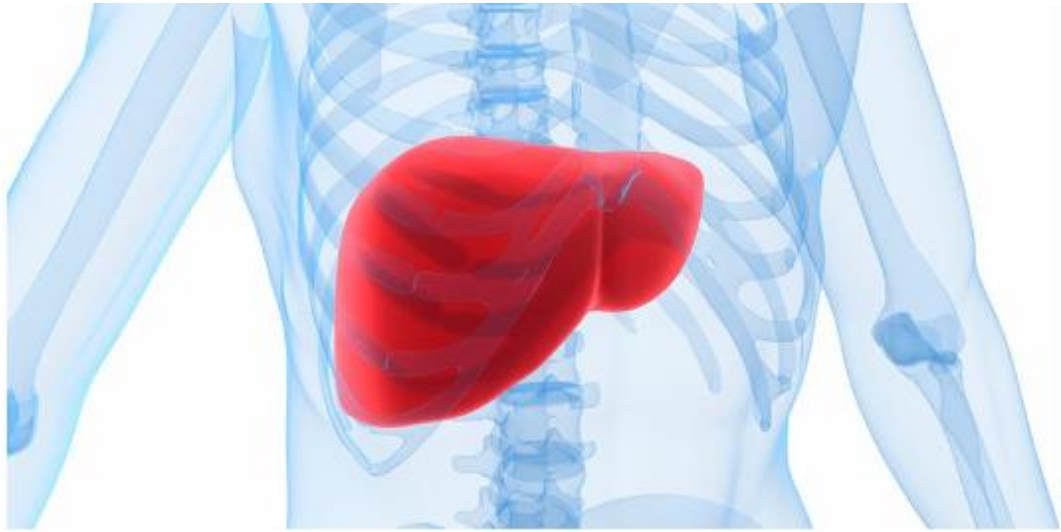


Liver pathology laboratory markers

Hepatocellular Damage	
AST	◦ Found in numerous tissues, including the liver, cardiac muscle, skeletal muscle, kidneys, brain, and pancreas
ALT	◦ Found primarily in the liver ▪ Considered most specific laboratory test for liver injury ▪ Release of enzymes into the blood occurs when liver-cell membrane is damaged
Biosynthetic Function (Proteins)	
Markers of nutrition	◦ Albumin (not liver specific but does mirror long-term hepatic synthetic function) ◦ Prealbumin ◦ Retinol binding protein
Alpha and beta globulins	◦ Alpha globulin ▪ Alpha-1-antitrypsin ▪ Ceruloplasmin ◦ Beta globulin ▪ Transferrin ▪ Sex hormone binding globulin
Coagulation factors	◦ Most factors are produced in the liver ◦ Factors II, VII, IX, and X are vitamin-K dependent (factors require adequate quantities of vitamin K for production of functional factors) ◦ PT is a collective measure of factors II, V, VII, and X

Excretory Function	
Serum bilirubin	◦ Heme product from catalysis and conjugation with glucuronic acid ◦ 3 fractions – conjugated, unconjugated, and delta bilirubin (albumin bound) ◦ Causes jaundice when concentrations exceed 1.5 mg/dL ◦ Conjugated hyperbilirubinemia indicates liver disease
Urine bilirubin	◦ Performed qualitatively using a urine dipstick
Blood ammonia	◦ Liver converts ammonia to urea – significant liver dysfunction results in elevated serum ammonia ◦ Poor correlation between ammonia level and degree of liver disease
Cholestasis	
ALP	◦ Isoenzymes include liver, bone, placental, and intestinal forms of ALP ◦ Usually increased during periods of growth (eg, children and teenagers) and during pregnancy
GGT	◦ Very sensitive indicator of liver injury (even minor injury) ◦ Clinical value – determine origin of elevated ALP
5′ NT	◦ Very sensitive and specific for hepatobiliary disease ◦ Clinical value – determine origin of elevated ALP

[2]Genzen JR, Slev, PR. Liver disease evaluation. ARUP consult. https://arupconsult.com/content/liver-disease-evaluation

Laboratory tests ordered

- **General labs**:
  - **Complete blood count:**
    - WBC: 19.46 k/uL (high)
    - Hgb 12.9 g/dL (low)
    - MCV 85.6 (normal)
    - Platelet 283 k/uL (normal)
  - **Coagulation (synthetic function):**
    - Prothrombin time 21.0 seconds (high)
  - **Plasma ammonia**: <44 umol/L (normal)
  - **Ceruloplasmin (Wilson):** 31 mg/dL (mild elevation)
  - **Alpha-1-antitrypsin:** 306 mg/dL (high)
  - **Complete metabolic panel (general chemistry):**
    - Protein 5.5 g/dL (low)
    - Albumin 2.1 g/dL (low)

    } Synthetic function

    - Total bilirubin 19.0 mg/dL (very high!)
    - Direct bilirubin 11.3 mg/dL

    } Excretory function

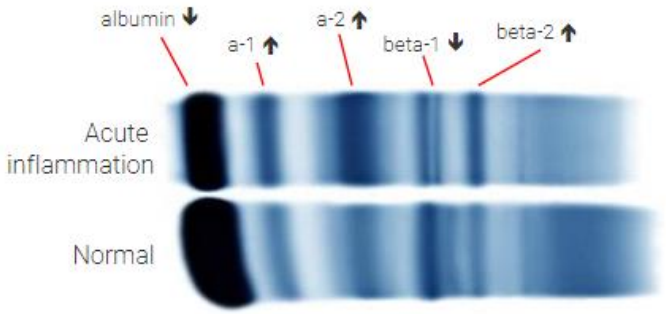
    - Alkaline phosphatase 159 U/L (mild elevation)
    - AST 159 U/L (high)
    - ALT 100 U/L (high)

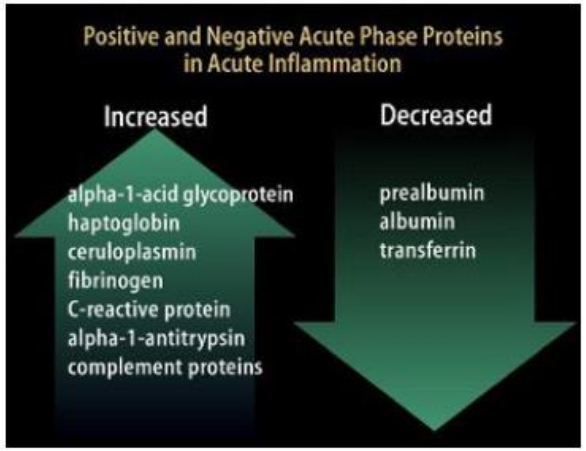
    } Hepatocellular damage

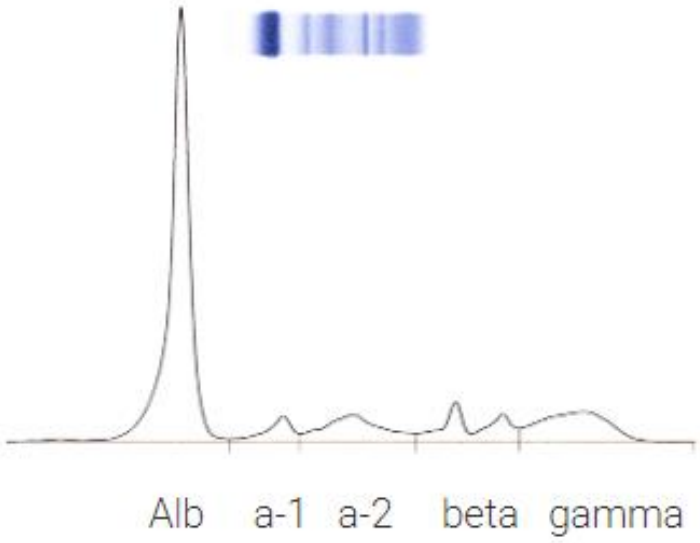
  - **Iron panel (hemochromatosis):**
    - Iron S/P 37 ug/dL (low)
    - TIBC 126 ug/dL (low)
    - Transferrin saturation 29% (normal)
    - Ferritin 1398 ng/mL (high)

    } Anemia of chronic disease

Protein electrophoresis







Total Protein:	7.4	g/dl	T.P. Ref. Range:	6.00 - 8.30 g/dL
Fractions	Rel %	g/dl	Ref. %	Ref. g/dl
Albumin	60.2	4.45	55.1 - 65.7	3.75 - 5.01
Alpha 1	4.5	0.33	3.1 - 5.6	0.19 - 0.46
Alpha 2	10.6	0.78	8.0 - 12.7	0.48 - 1.05
Beta	10.4	0.77	8.5 - 12.8	0.48 - 1.10
Gamma	14.3	1.06	10.3 - 18.2	0.62 - 1.51

Images courtesy of Dr. Julio Delgado

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Interpretation: Acute liver damage is present with very high bilirubin, AST>ALT

Liver disease differential diagnosis

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Immunology laboratory tests

- ANA with HEp-2 Substrate IgG by IFA:
  - Nuclear pattern: negative
  - Speckled cytoplasmic pattern: Positive, 1:160 titer
- Method:
  - Commercially available HEp-2 substrate slides
  - Add patient serum and then IgG conjugate antibody with fluorescein dye
- Background:
  - Antinuclear antibodies are autoantibodies to structures in the nucleus, cytoplasm, and mitotic apparatus
  - Associated with different systemic autoimmune rheumatic diseases, but also seen in other conditions
  - ANA is a good screening method, but not specific
  - Report the titer and pattern by IFA

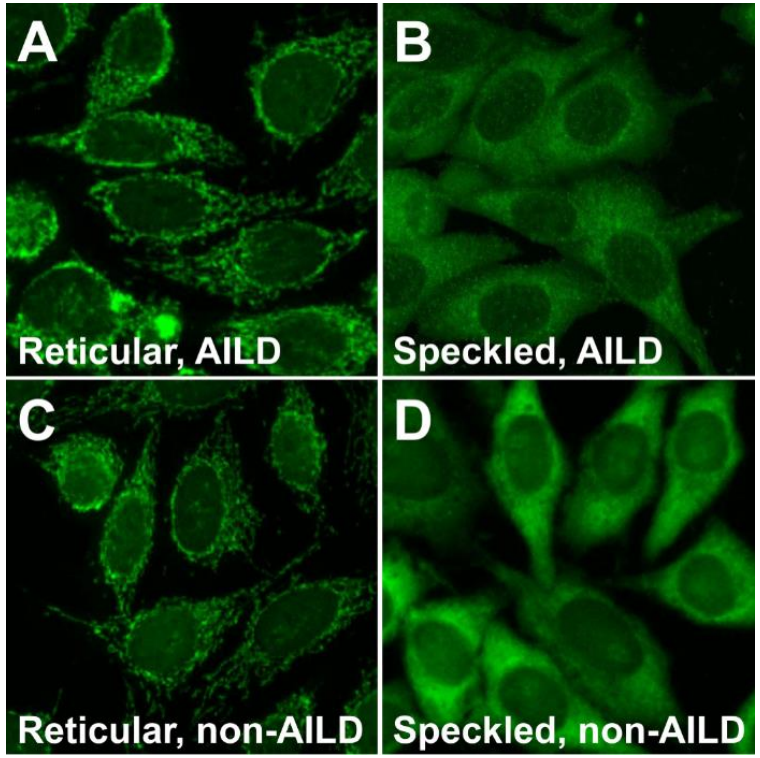

Image from [3]PMID: 33411840

Images from werfen.com

Immunology laboratory tests

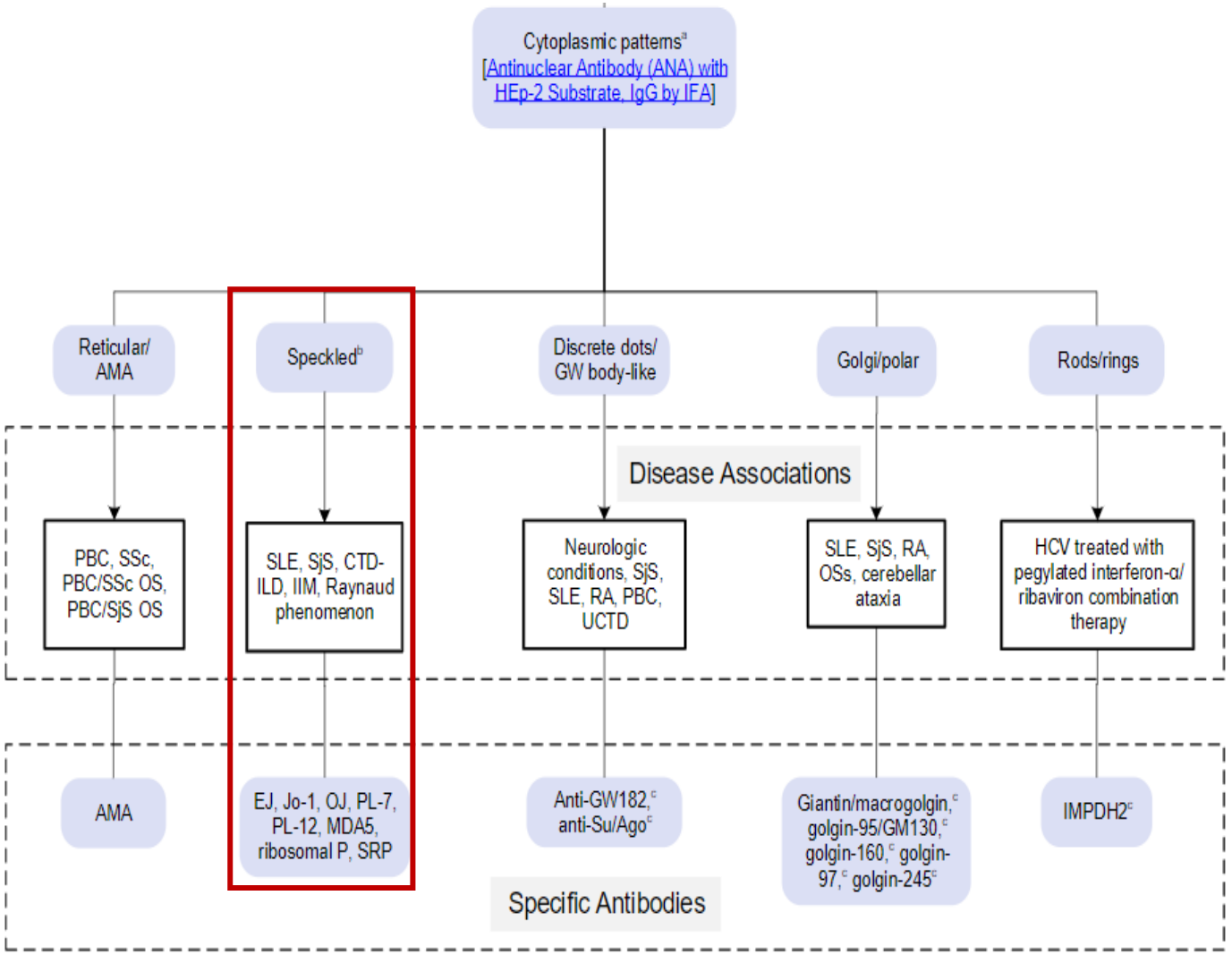

Image from arupconsult.com

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Immunology laboratory tests

- **Antibodies related to autoimmune hepatitis**:
  - F-actin (smooth muscle) antibody, IgG: 63 (Ref 0-19)
  - F-actin antibody, IgA: 67.1 (Ref 0-24.9)
  - Smooth muscle antibody, IgG: 1:160 (Ref <1:20)
  - Liver-Kid Microsome antibody, IgG: <1:20
  - Mitochondrial antibody, IgG: 73.6 (Ref 0-24.9)
- Overall serum IgG: 1408 mg/dL (normal)

***The presence of autoantibodies (even high titer) are not diagnostic of disease and should always be correlated with other laboratory results and overall clinical picture of the patient.**

Simplified Diagnostic Criteria for AIH

Variable	Cutoff	Points
IgG	Above upper limit	1
	>1.10 times upper limit of normal	2
Liver histology	Compatible with AIH	1
	Typical of AIH	2
Absence of viral hepatitis	Yes	2
ANAs or SMAs[a]	≥1:40	1
	≥1:80	2
Anti-LKM[a]	≥1:40	2
Anti-SLA[a]	Positive	2

Results

Diagnosis	Cutoff (Points)
Probable AIH	6
Definite AIH	≥7

Simplified International Autoimmune Hepatitis Group (IAIHG) criteria from arupconsult.com

[3]Cha HJ, Hwang J, Lee LE, Park Y, Song JJ. The significance of cytoplasmic antinuclear antibody patterns in autoimmune liver disease.

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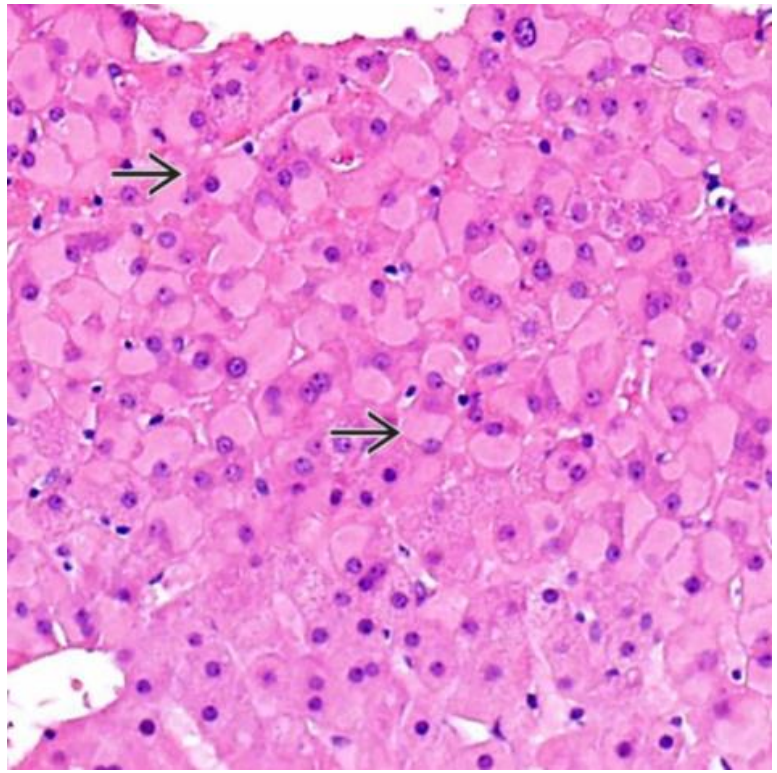
Infectious disease laboratory tests ordered

- Acute hepatitis virus panel:
  - Hepatitis A antibody, IgM: Negative
  - Hepatitis B:
    - Core antibody, IgM: Negative
    - Surface antigen: Negative
  - Hepatitis C antibody by CIA: Negative, 0.41
- Epstein-Barr Virus (EBV)
  - Antibody to nuclear antigen, IgG: >600 (Ref 0-21.9)
  - Antibody to early antigen, IgG: <5.0 (normal)
  - Viral capsid antigen, IgM: 58.5 (Ref 0-43.9)
  - Viral capsid antigen, IgG: >750 (Ref 0-21.9)
  - PCR: Positive



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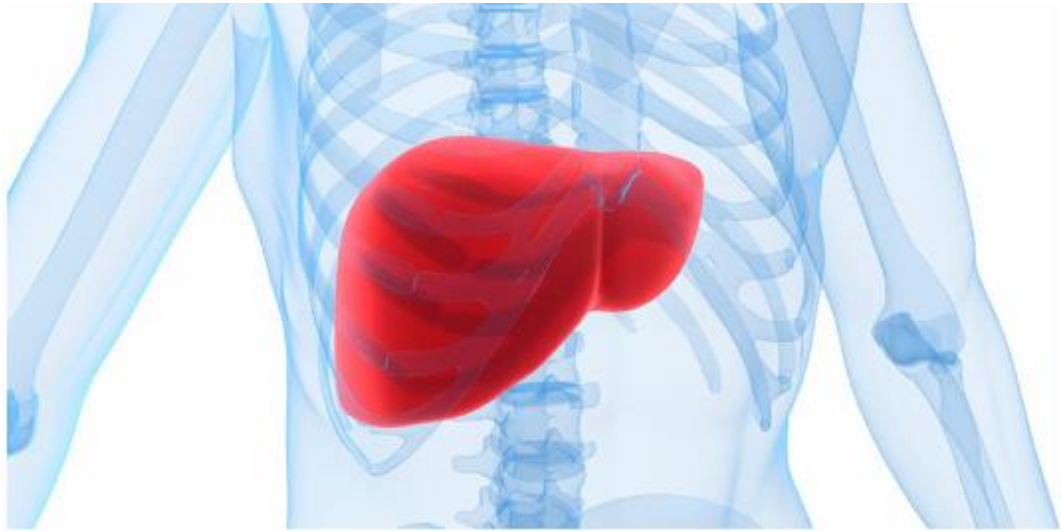
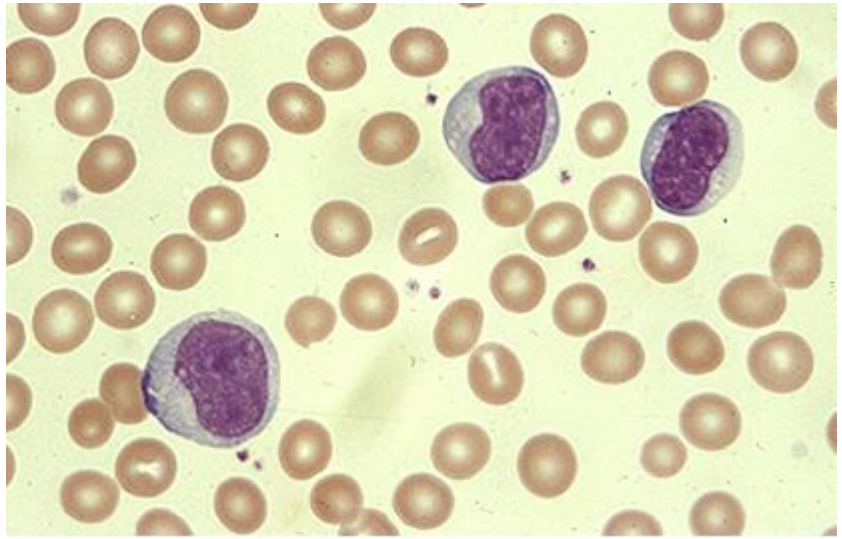


Epstein-Barr Virus (EBV)

- Also known as Human Herpesvirus 4
- Double-stranded DNA virus
- Worldwide distribution with EBV-seropositivity in approximately 90-95% adults
- Most infections are subclinical
- **Infectious Mononucleosis**: “Kissing disease”
  - Spread through saliva, mostly in young adults
  - Fever, adenopathy, pharyngitis, **splenomegaly**
  - EBV infects oropharyngeal epithelial cells, B cell, monocytes, and **T cells (CD8+ T cells in blood)**
  - Life-long latency in B cells



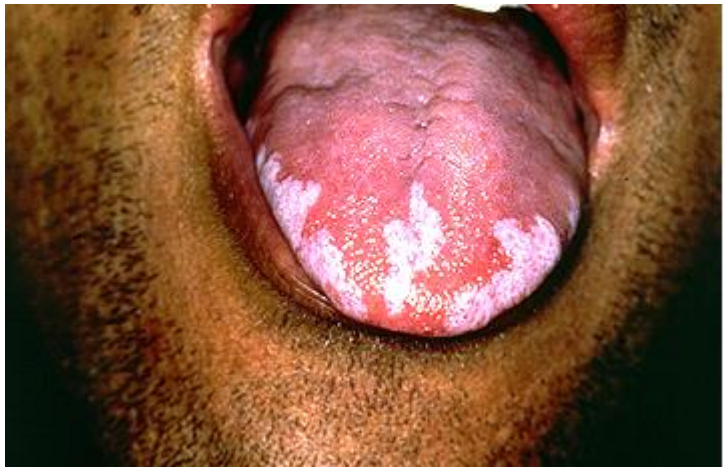
Signs	
Adenopathy	100
Fever	80 to 95
Pharyngitis	65 to 85
Splenomegaly	50 to 60
Bradycardia	35 to 50
Periorbital edema	25 to 40
Palatal enanthem	25 to 35
Liver and spleen tenderness	15 to 30
Hepatomegaly	15 to 25
Rhinitis	10 to 25
Jaundice	5 to 10
Skin rash	3 to 6
Pneumonitis	<3

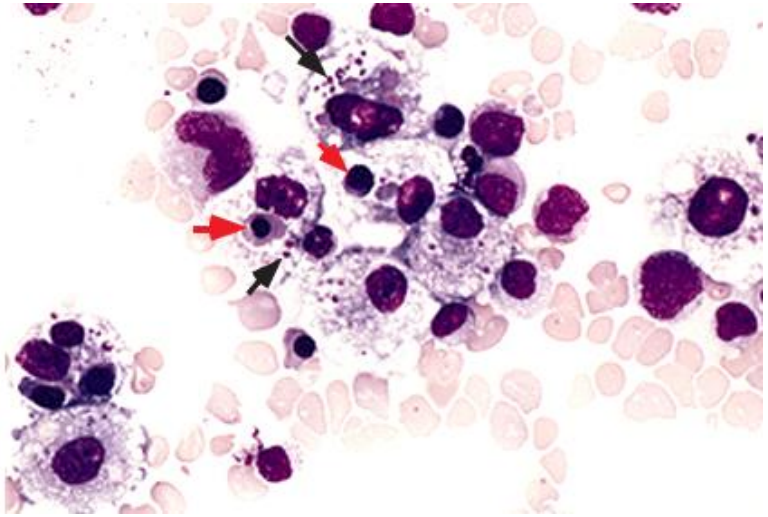
Images from UpToDate.com

[4]Aronson, MD and Auwaerter PG. Infectious mononucleosis. UptoDate.

Other clinical findings and sequelae of EBV

- Acute infection (IM):
  - Hemolytic anemia: “Cold agglutinin” IgM Anti-i antibody to fetal RBCs
  - EBV can affect basically any organ system and cause disease (including liver)
- Chronic/delayed complications:
  - Oral hairy leukoplakia (usually immunocompromised)
  - Lymphoproliferative disorders
    - Hemophagocytic lymphohistiocytosis
    - B cell and T cell lymphomas
    - Post-transplant lymphoproliferative disorder
    - Nasopharyngeal carcinoma





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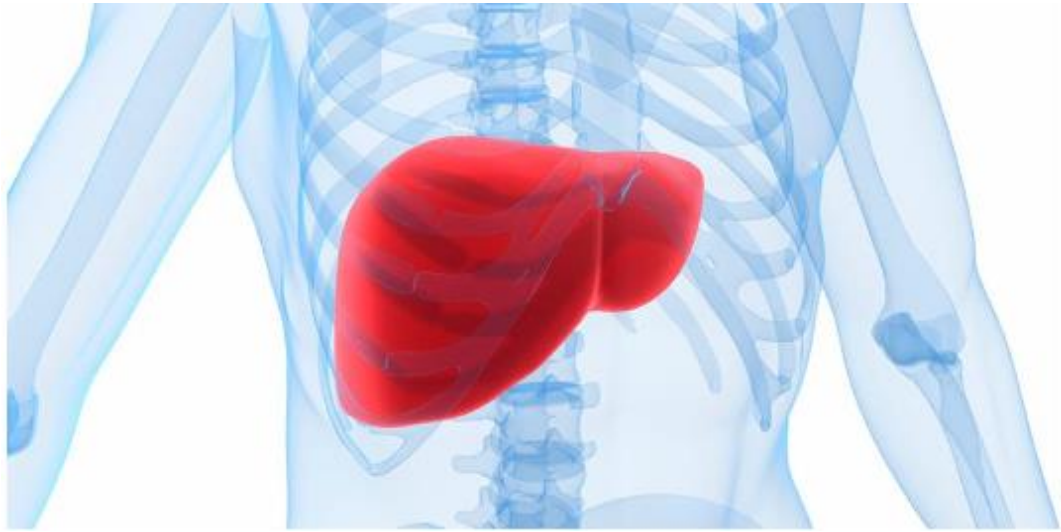
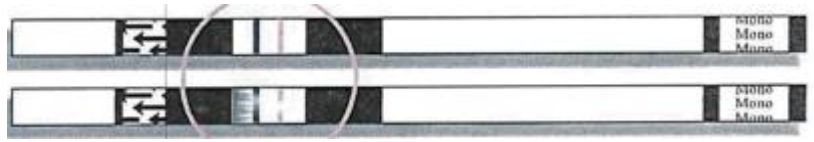


EBV laboratory testing

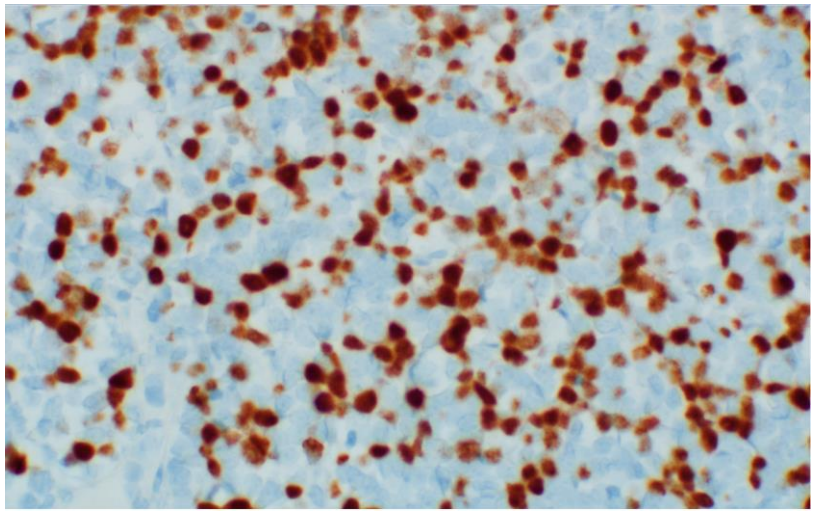
- **Infectious Mononucleosis rapid test:**
  - Primary EBV infection of B cells induce the production of antibodies directed against viral and unrelated antigens found on bovine RBCs
  - Use bovine erythrocytes to detect the presence of heterophile antibodies
  - Rapid tests use immunochromatographic dipstick technology with a strip that has bovine erythrocyte extract coated on the membrane

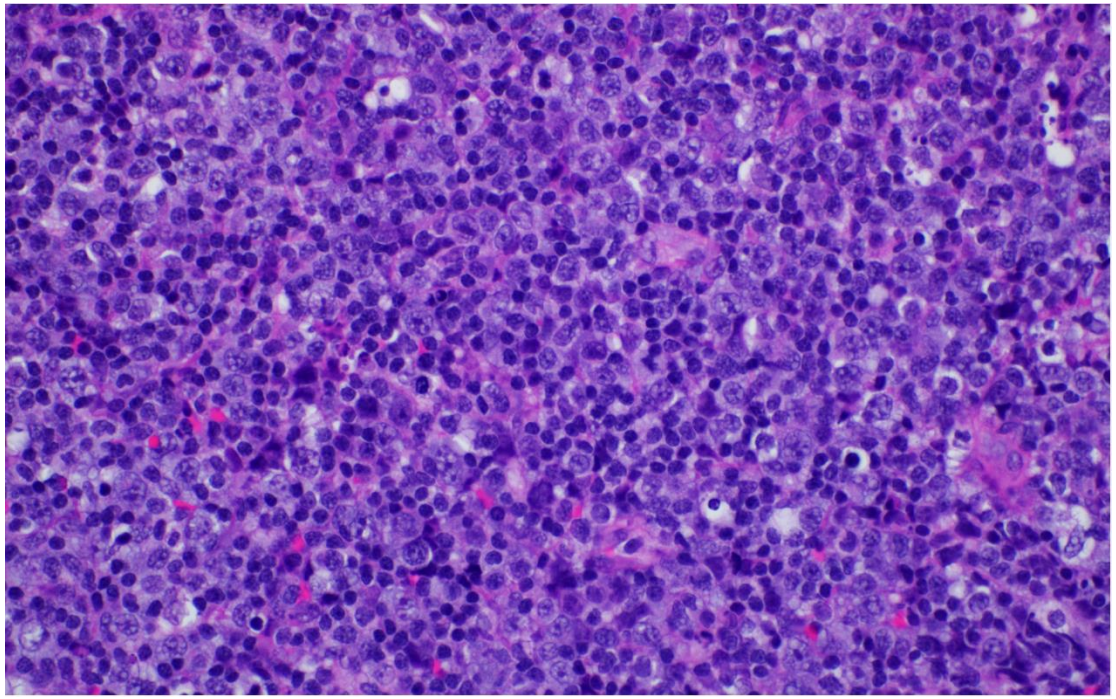


  - Mix the patient serum with a diluent, add absorbent end to this mixture
  - In 5 minutes, a heterophile antibody will complex with the bovine RBC extract conjugated color particles in the mixture and also with bovine RBC extract on the membrane (IgM antibodies are pentamers)

EBV In-situ Hybridization (ISH)

- EBV ISH is used to detect viral RNA in infected cells in tissue biopsy samples using nucleotide specific probes
- The probes hybridize with the specific EBER RNA sequences and a color is produced (DAB/Peroxidase)





Images courtesy of Dr. Anton Rets

EBV laboratory testing

- **EBV PCR**:
  - Can be useful early in a case of infectious mononucleosis when false negative results can happen for the heterophile antibody test
  - However, a positive PCR does not distinguish between IM and reactivation
  - Viral genomes can be detected in 40-70% of patients at symptom onset
- **EBV specific antibodies:**
  - Useful in separating out acute vs. latent vs. reactivation
  - Longer turn-around time
  - Usually done if the patient has a negative heterophile antibody test
  - Young children often have a negative heterophile antibody test

[4]Aronson, MD and Auwaerter PG. Infectious mononucleosis. UpToDate.

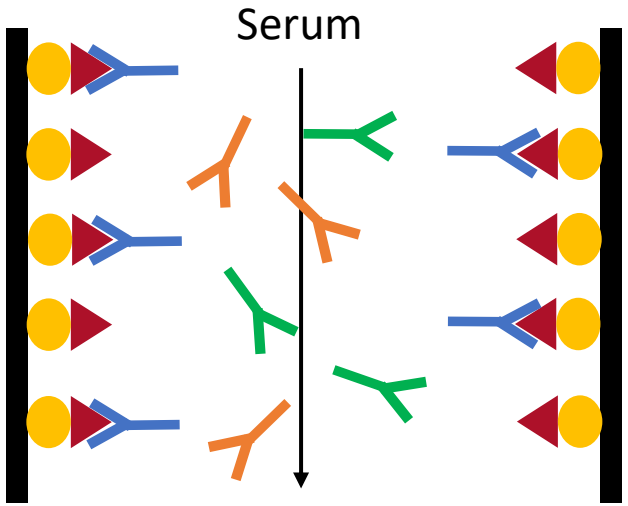
[5]Hillyard, DR, Slev PR. Epstein-Barr Virus – EBV. ARUP consult. https://arupconsult.com/content/epstein-barr-virus

EBV specific antibody testing

- Nuclear antigen (EBNA), IgG: >600
- Early antigen (EA), IgG: <5.0
- Viral capsid antigen (VCA), IgM: 58.5
- Viral capsid antigen (VCA), IgG: 750

METHOD:

- Indirect Chemiluminescent immunoassay
  - Use magnetic particles coated with the antigen (EBNA, EA, VCA) as solid phase
  - Mouse anti-human IgG with isoluminol



Interpretation of EBV-Specific Serologic Results				
Infection	**VCA IgM**	**VCA IgG**	**EA**	**EBNA**
No previous	Negative	Negative	Negative	Negative
Acute/primary	Positive	Positive	Positive/negative	Negative
Recent	Positive/negative	Positive	Positive/negative	Positive/negative
Past	Negative	Positive	Negative	Positive
Reactivation[a]	Positive/negative	Positive	Positive	Positive

Table from arupconsult.com

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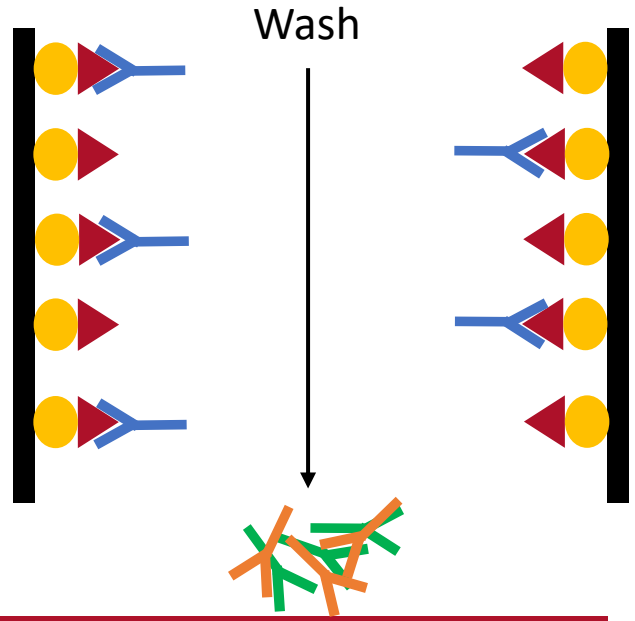

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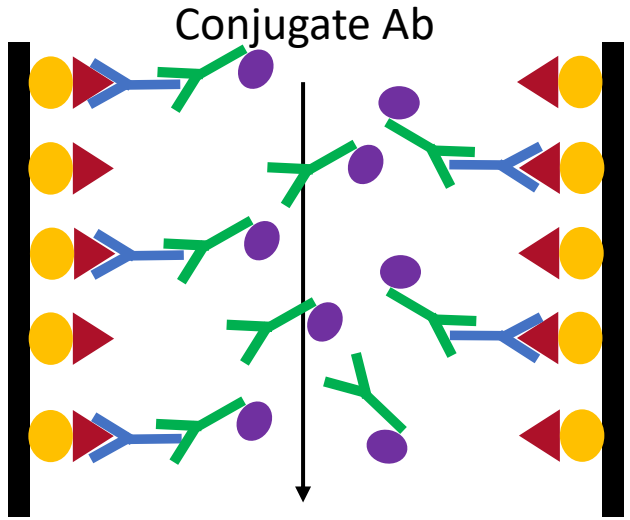

Measure isoluminol derivative light signal with a photomultiplier

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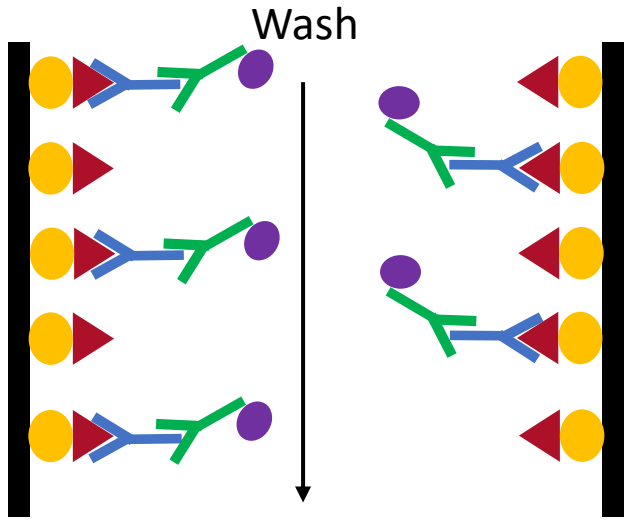

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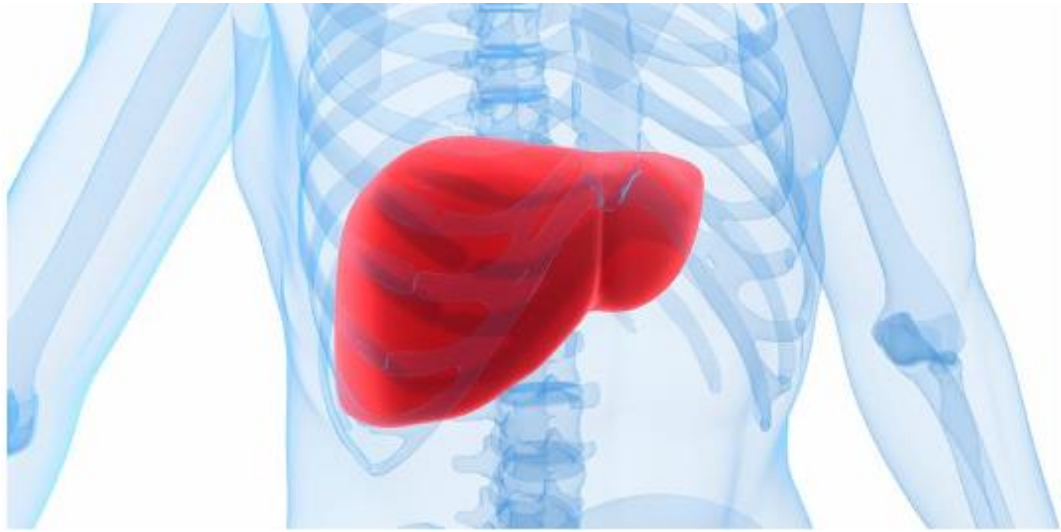
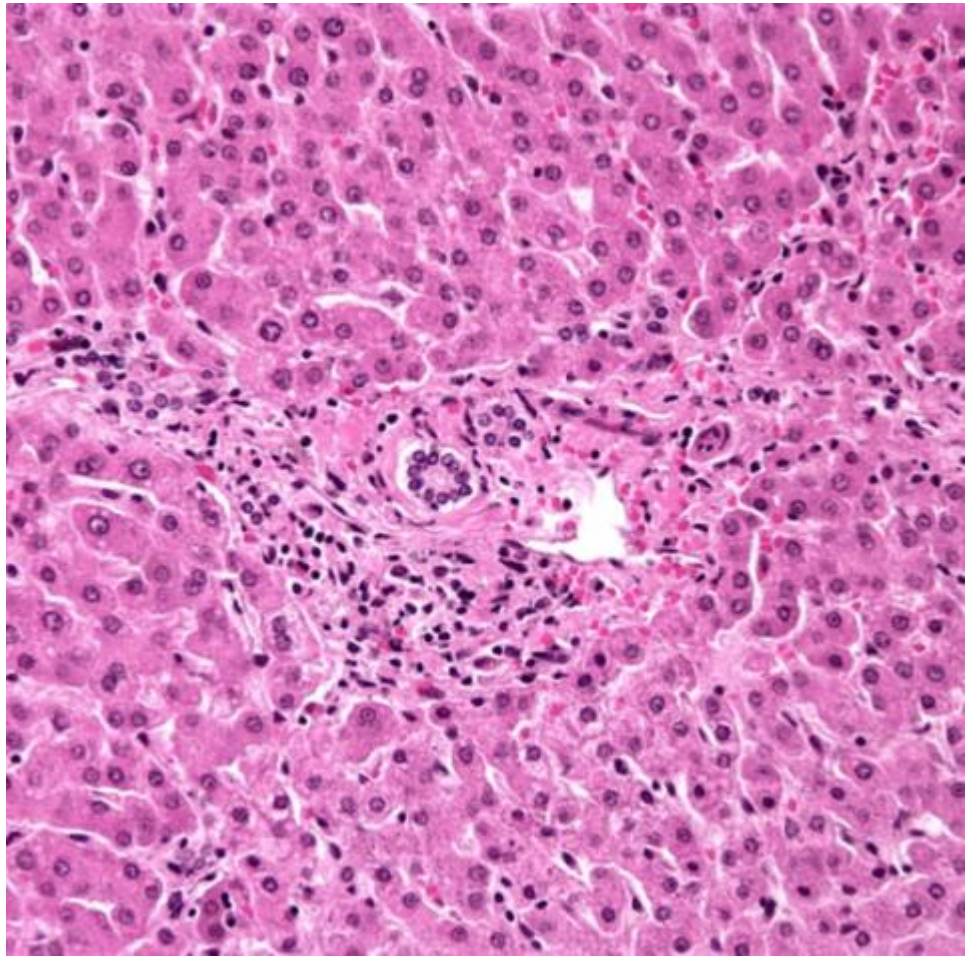


Liver disease differential diagnosis

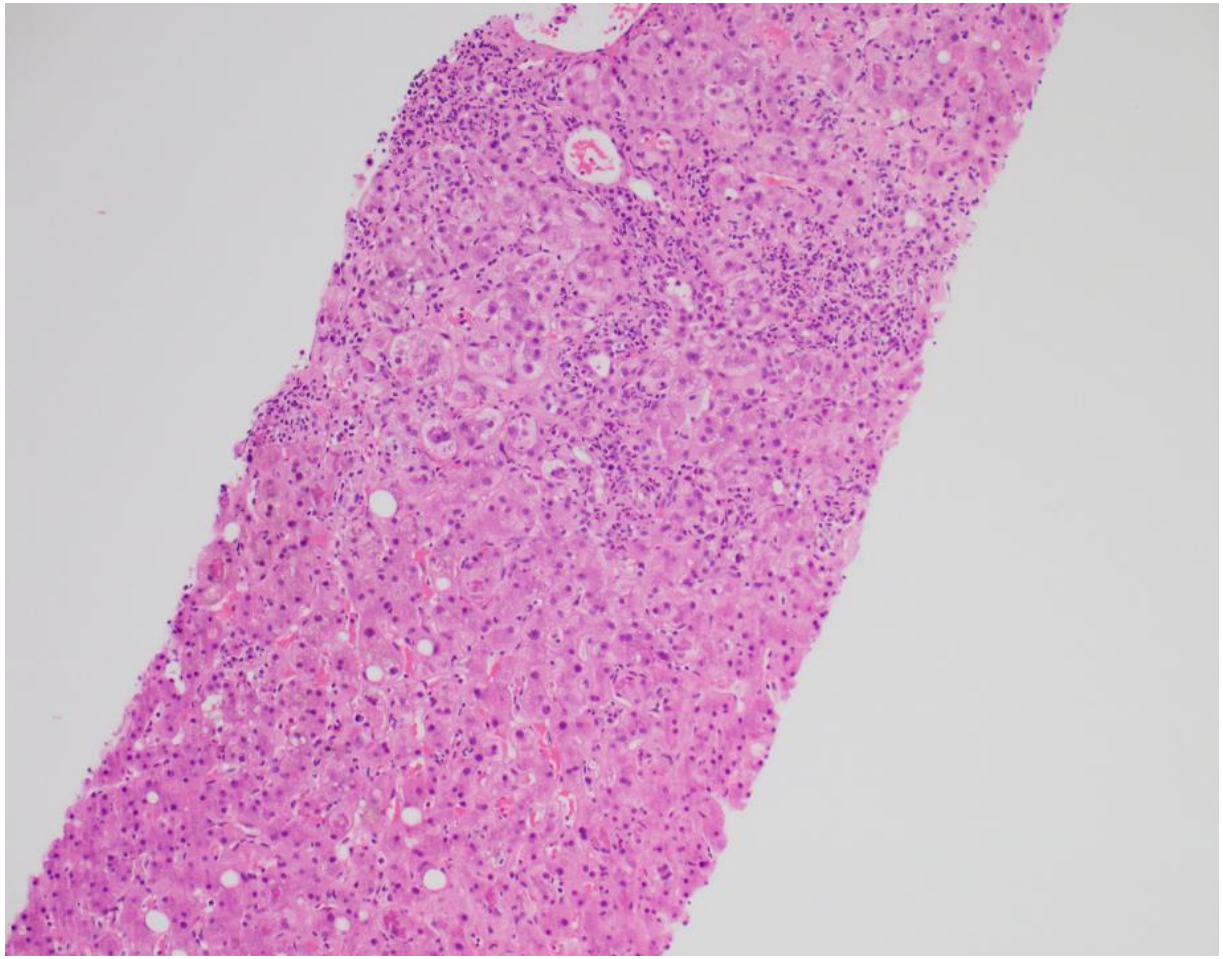
- **Autoimmune**
  - **Primary biliary cirrhosis**
  - Primary sclerosing cholangitis
  - **Autoimmune hepatitis**
- Genetic
  - Wilson disease
  - Alpha-1-antitrypsin deficiency
  - Hemochromatosis
  - Crigler-Najjar syndrome
- **Viral Infection**
  - Hepatitis A, B, C, or D
  - Cytomegalovirus (CMV)
  - **Ebstein-Barr virus (EBV)**
  - Herpes Simplex virus (HSV)
- Nonalcoholic liver disease
  - Congestive heart failure
  - Biliary disease
  - Nonalcoholic steatohepatitis
- **Toxins**
  - **Alcohol**
  - Aflatoxin
  - Acetaminophen
  - **Other drugs**
- Hematologic syndromes
  - HELLP
  - Ischemia
  - Budd-Chiari syndrome

[2]Genzen JR, Slev, PR. Liver disease evaluation. ARUP consult. https://arupconsult.com/content/liver-disease-evaluation

Liver biopsy

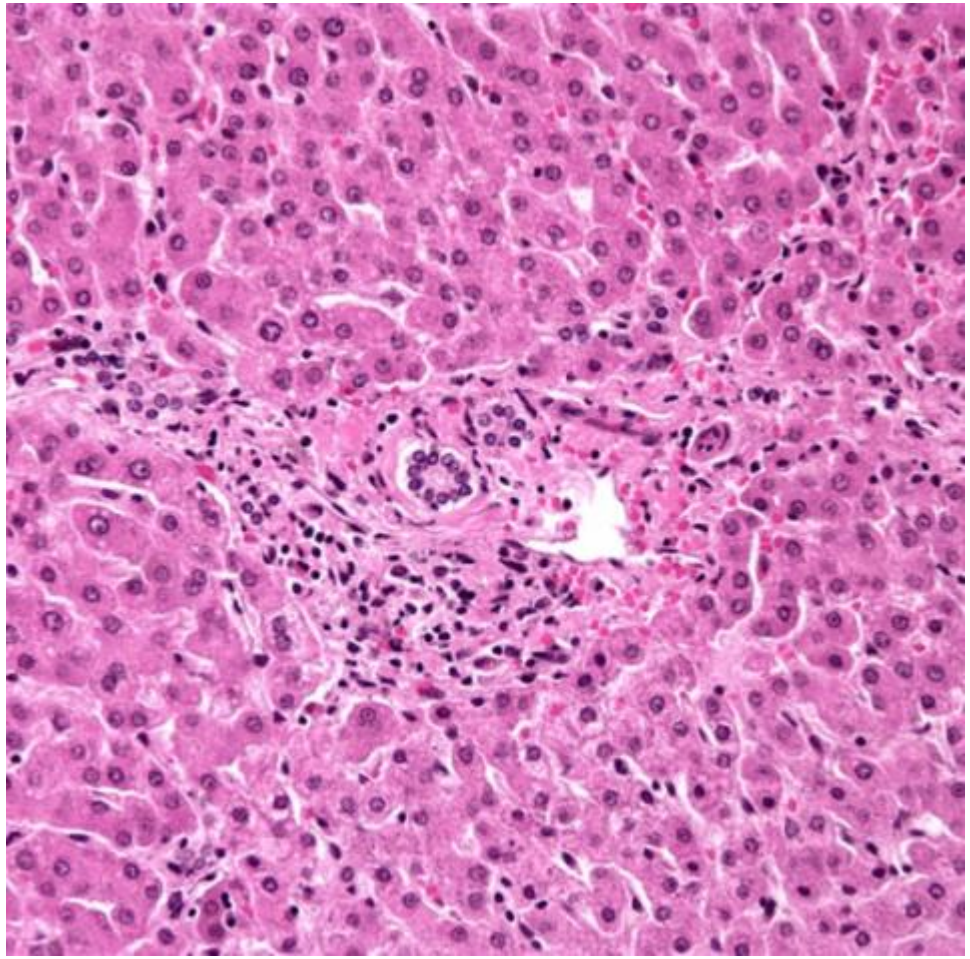


Normal Liver (Image from Expertpath.com)



Patient liver biopsy at low power

Liver biopsy



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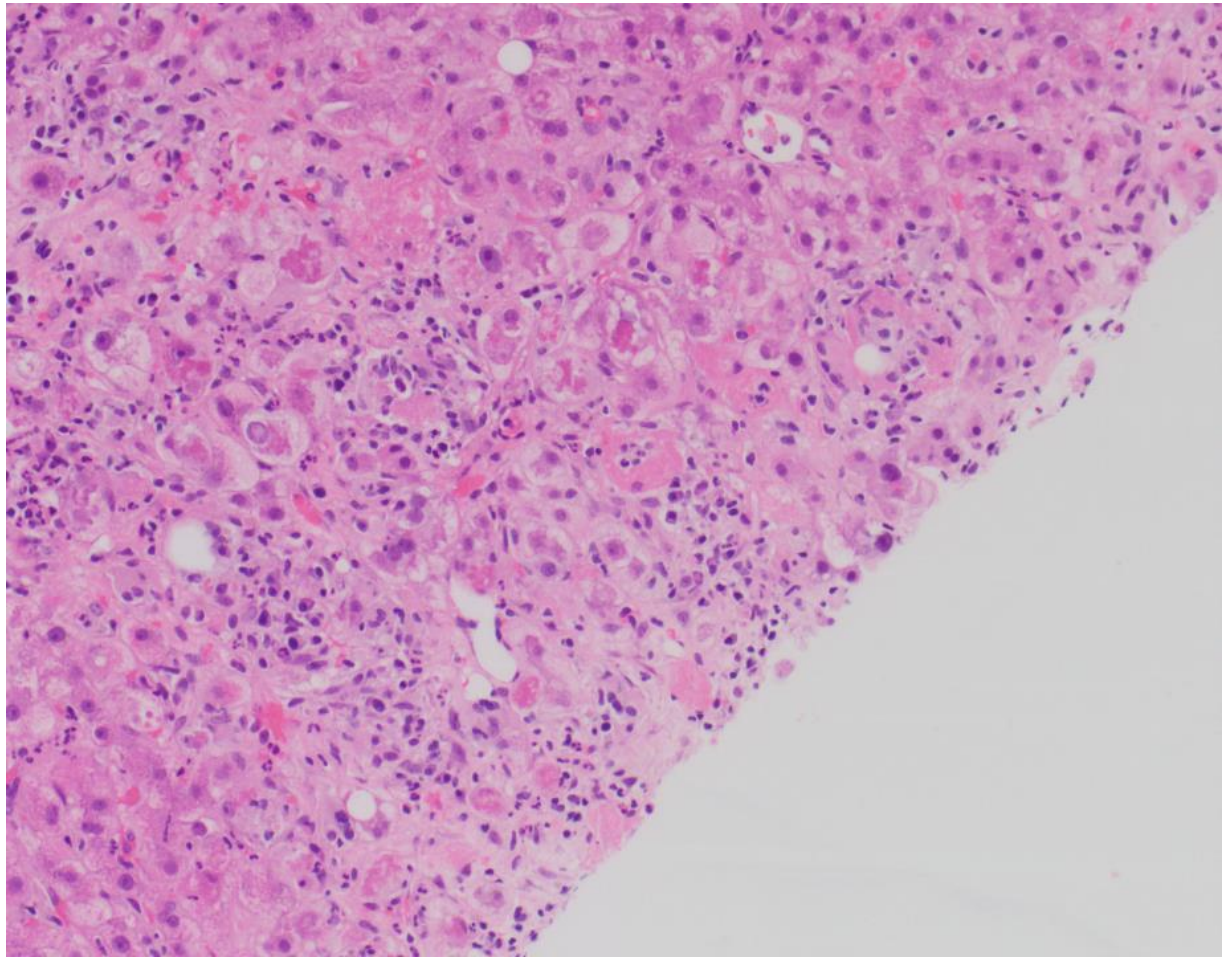
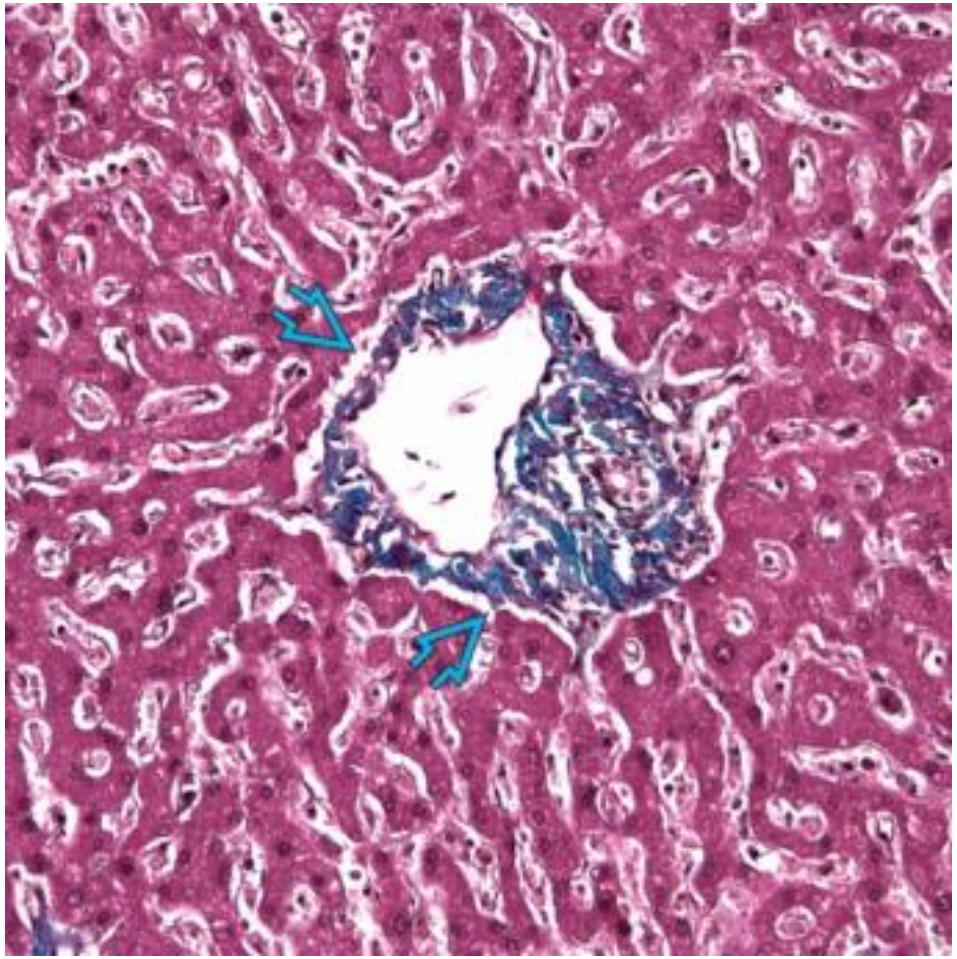
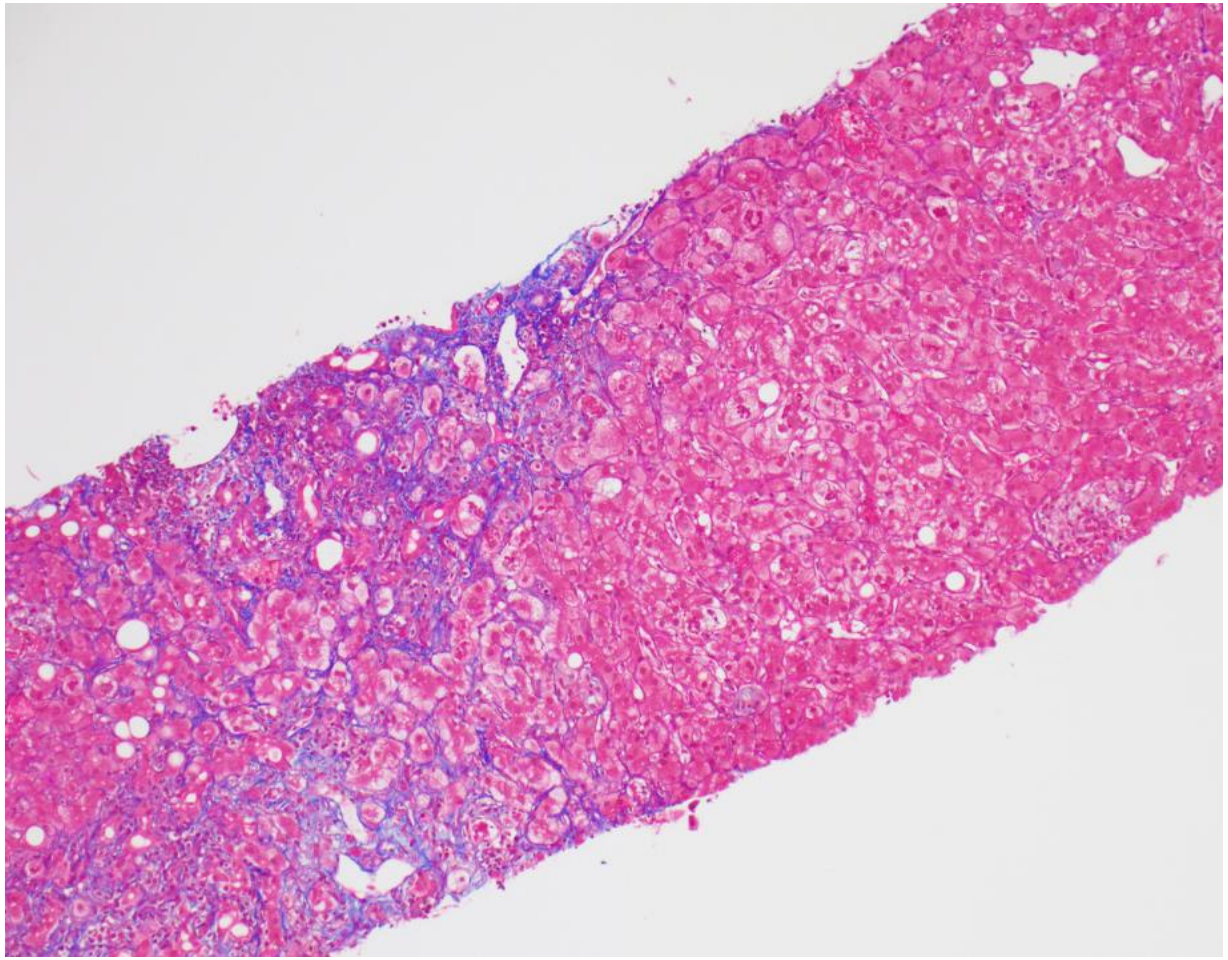


Patient liver biopsy at high power

Liver biopsy



Normal Liver (Image from Expertpath.com)



Trichrome stain for fibrosis

Liver biopsy pathology

- Active and chronic steatohepatitis with advanced fibrosis
  - Hepatocyte ballooning with intracellular Mallory-Denk bodies (Alcohol)
- Patchy portal and lobular plasma cells (seen with drug-induced liver injury and autoimmune hepatitis)
- **Fibrin ring granulomas**: Can be seen with ***Coxiella burnetti*** **(Q fever)**, EBV, CMV, among other etiologies
- EBV In-situ hybridization (ISH): Negative
- CMV immunohistochemistry: Negative

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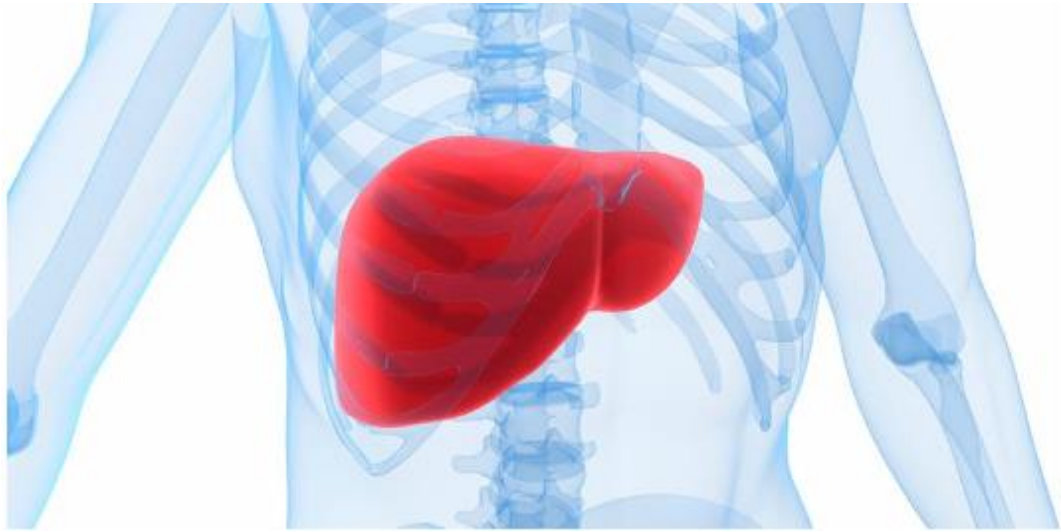

Q fever serology by IFA

- **Phase I IgM:** Positive, 1:256
- **Phase I IgG:** Positive, 1:512
- **Phase II IgM:** Positive, 1:4096
- **Phase II IgG:** Positive, >1:131072

- **Interpretation:** Antibodies to Phase II antigens > Phase I antigens, compatible with **Acute Q fever**

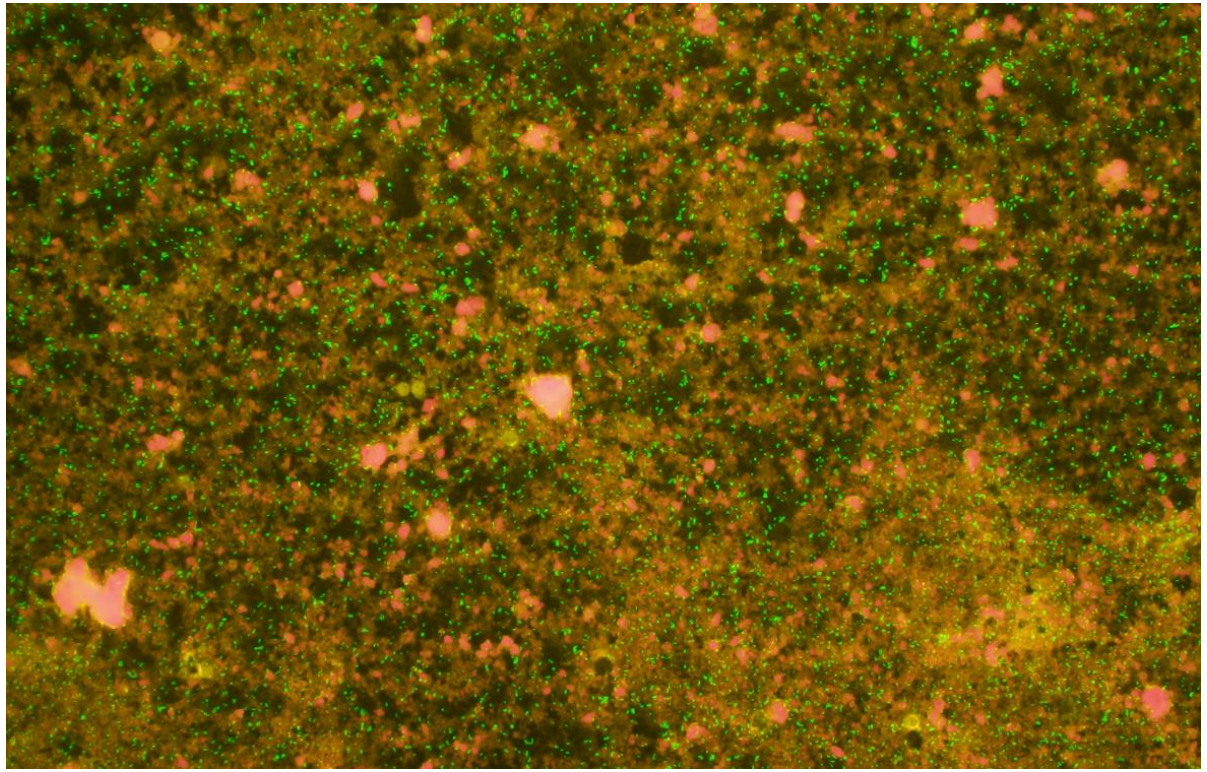

Image courtesy of the Microbial Immunology II lab

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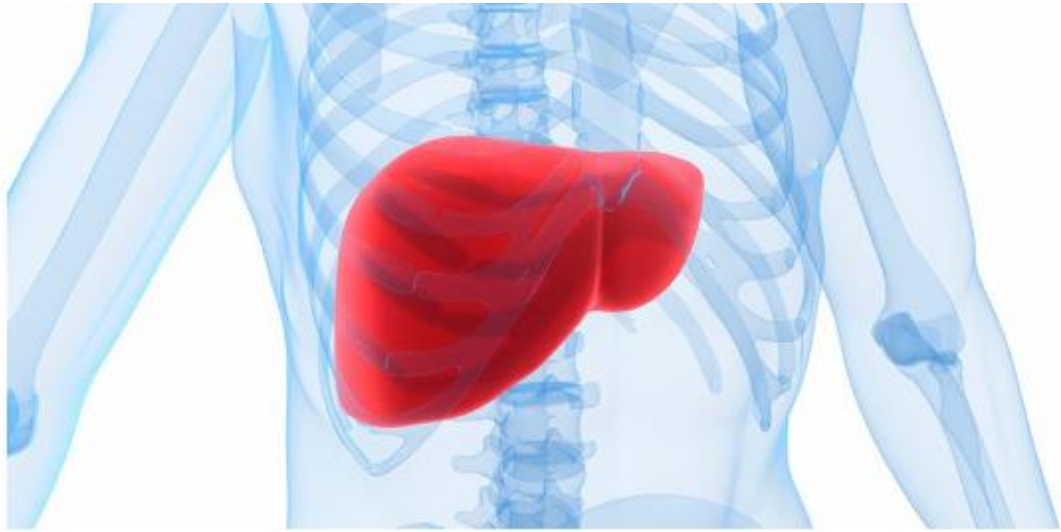


Q fever

- Q fever is the disease caused by the bacteria *Coxiella burnetii*
- Zoonotic disease typically acquired from farm animals (cattle, sheep, and goats), other reservoirs include birds, turtles, and arthropods (ticks)
- First recognized as a human disease in Australia in 1935 during an outbreak in workers in a slaughterhouse
- Initially called “Q fever” for “query” because the cause was unknown.

Image from theguardian.com

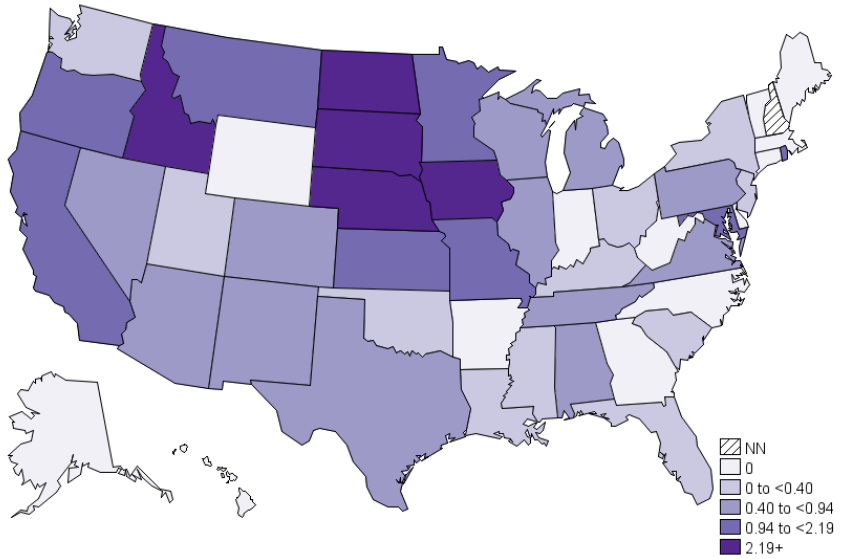
[6]Jackson, Brian. Coxiella burnetti – Q fever. https://arupconsult.com/content/coxiella-burnetii

[7]https://www.cdc.gov/qfever/stats/index.html

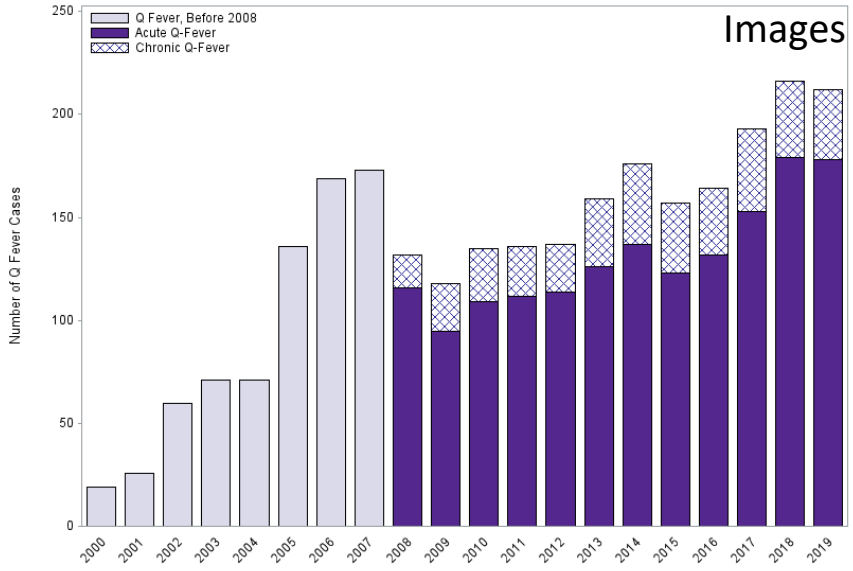
Epidemiology

- Geographic distribution of Q fever is worldwide with few exceptions such as New Zealand
- In the US, Q fever was discovered in the 1940s and became a nationally notifiable disease by 1999.
- Cases of Q fever in the US have been increasing since 2000.
- Most cases are in the western and plains states
  - Spring and early summer months during birthing season for cattle, sheep, and goats

Annual incidence (per million population) of reported Q fever–United States, 2019.
(NN= Not notifiable)



Number of reported cases of Q fever –United States, 2000–2019



Images from cdc.gov

[?https://www.cdc.gov/qfever/stats/index.html](https://www.cdc.gov/qfever/stats/index.html)

Epidemiology

- Individuals with highest risk:
  - Persons in contact with farm animals (ranchers, farmers, veterinarians…)
  - Individuals living downwind from farms
  - Laboratory personnel
  - Slaughterhouse workers
- More common in men and older people

Average annual incidence (per million population) of reported Q fever, by age group – United States, 2019

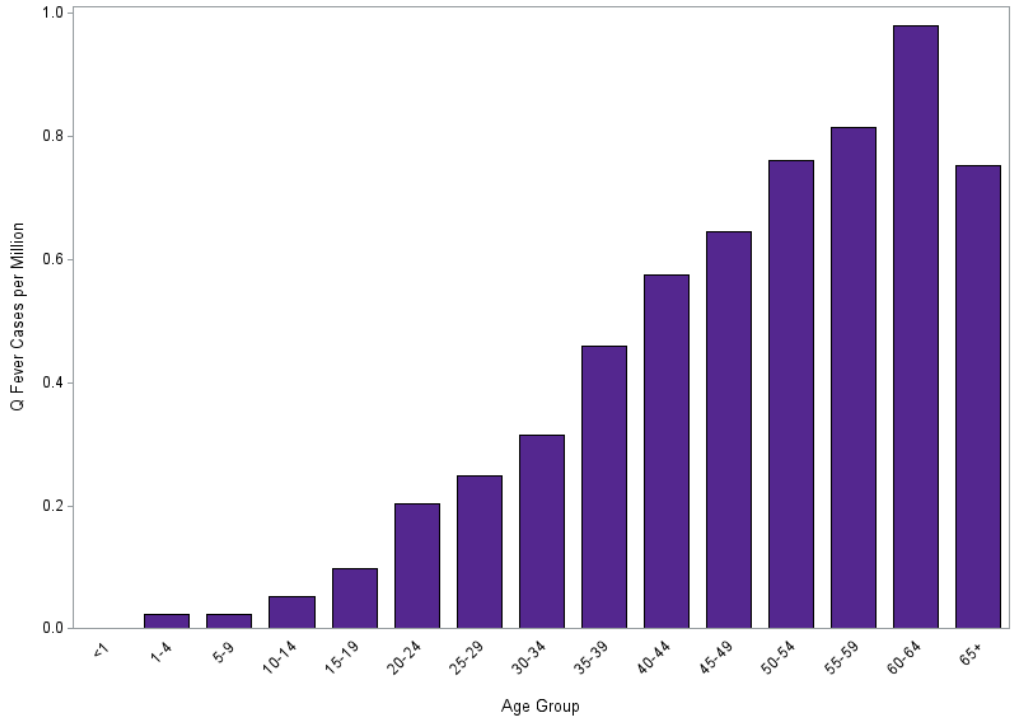


Image from cdc.gov

[8]Raoult, Didier. Microbiology and epidemiology of Q fever. UpToDate.

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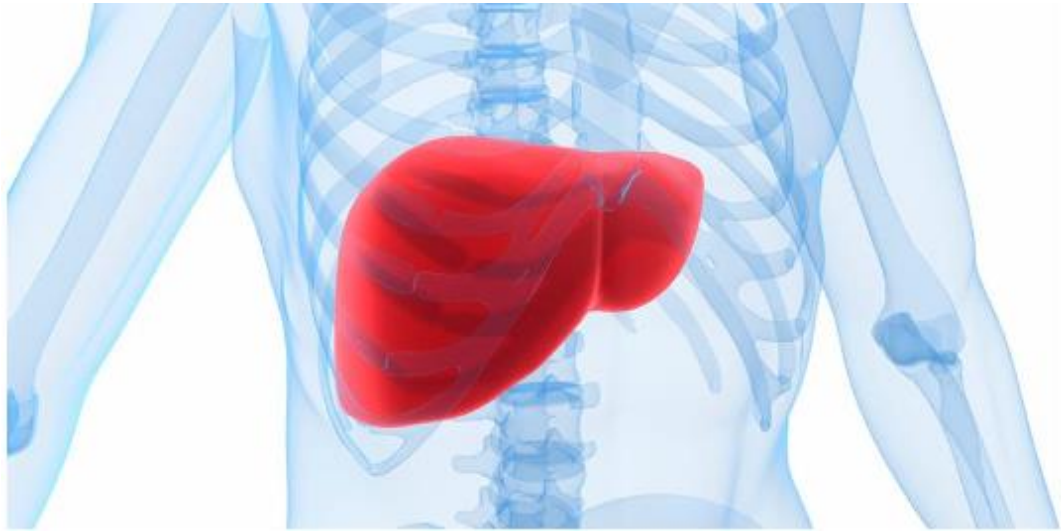

Transmission

- People who become infected usually do so after contact with infected animal
  - *Coxiella* is usually found in animal feces, urine, milk, and birth products
- Breathing in dust (aerosol) from the environment that has *Coxiella* (range can be miles)
- Eating contaminated unpasteurized dairy products
- Rare reports of blood transfusion, mother-to-fetus, and sexual transmission
- Potential agent of bioterrorism

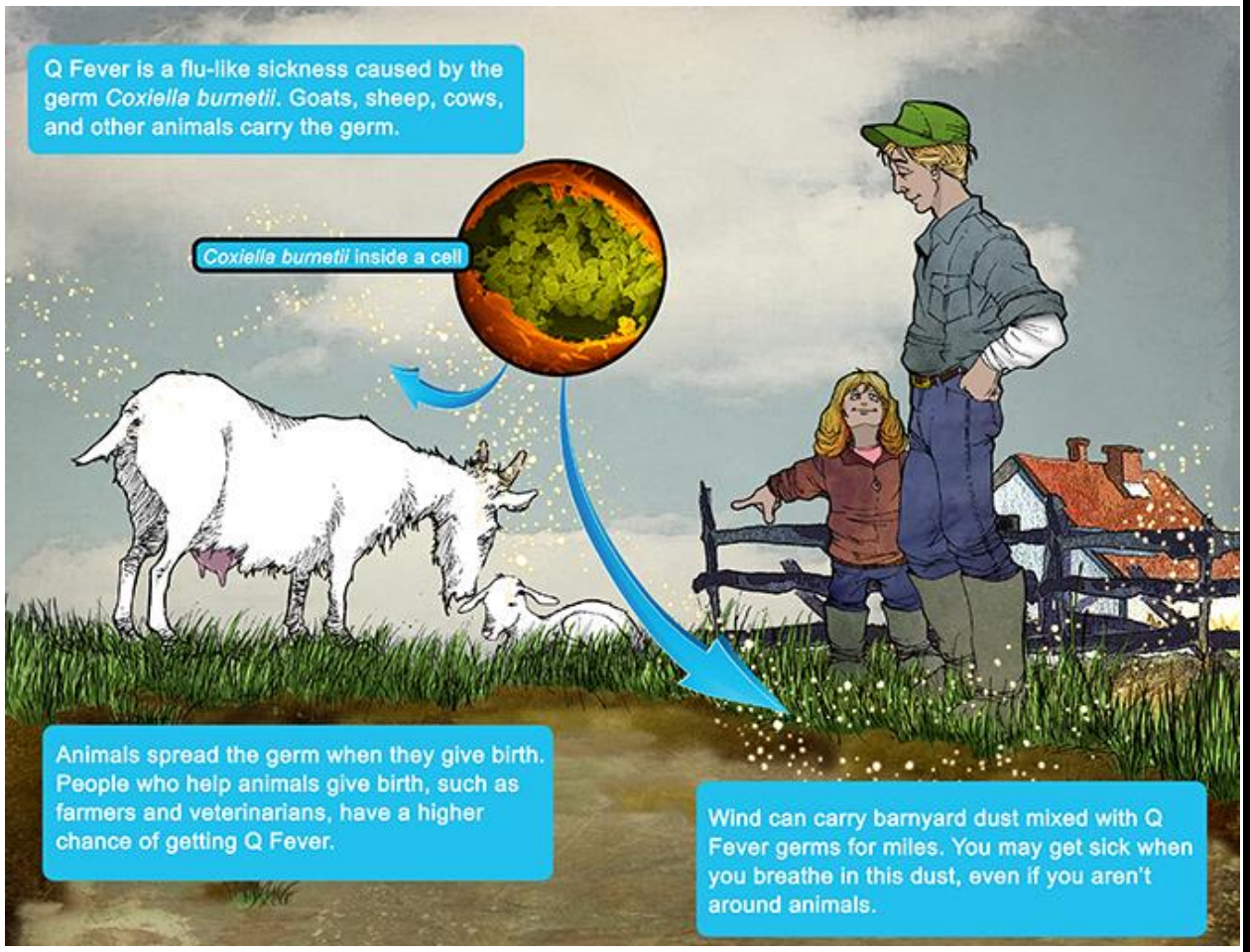

Image from cdc.gov

[8]Raoult, Didier. Microbiology and epidemiology of Q fever. UpToDate.

Clinical Manifestations of Acute Q fever

- Incubation period: approximately 20 days
- **Acute infection:** self-limited "flu-like illness"
  - High grade fever, fatigue, headache, myalgias, nausea/vomiting
  - Some patients may experience more serious illness with pneumonia, hepatitis (most common), myocarditis, or CNS complications
- Estimated half of infected people are asymptomatic
- Pregnant women have increased risk of miscarriage, preterm delivery, or low infant birth weight

[9]Raoult, Didier. Clinical manifestations and diagnosis of Q fever. UpToDate.

Clinical Manifestations of Chronic Q fever

- **Chronic infection:** Persistent localized infections after acute Q fever infection.
  - Occurs in 1-5%, usually immunocompromised, underlying valvular/vascular disease, pregnancy, or prosthetic joints
  - Can present within weeks to years after initial acute infection.
- **Clinical Manifestations**:
  - Most common manifestation is endocarditis which is fatal if left untreated
  - Vascular aneurysms
  - Liver disease
  - Lymphadenitis/lymphoma
  - Bone/joint infections

[9]Raoult, Didier. Clinical manifestations and diagnosis of Q fever. UpToDate.

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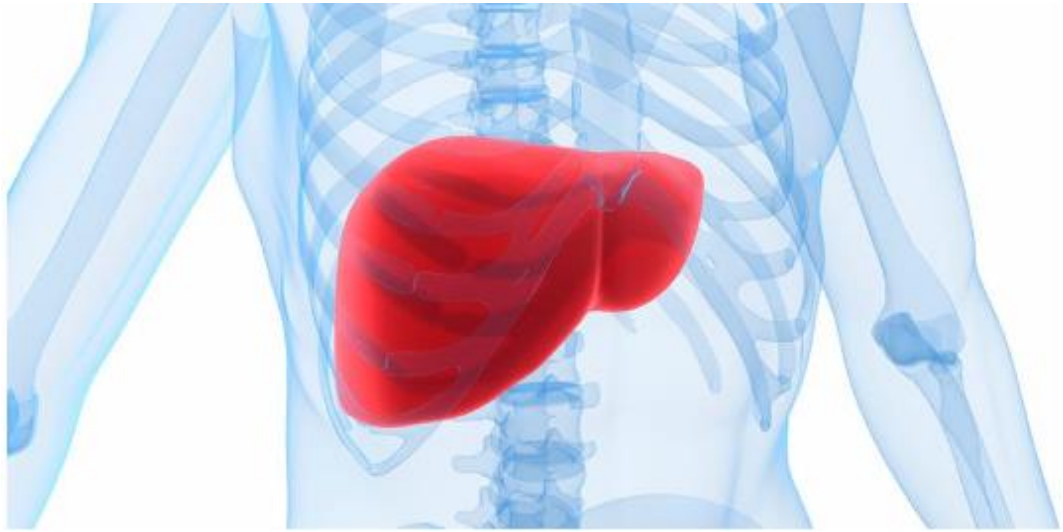


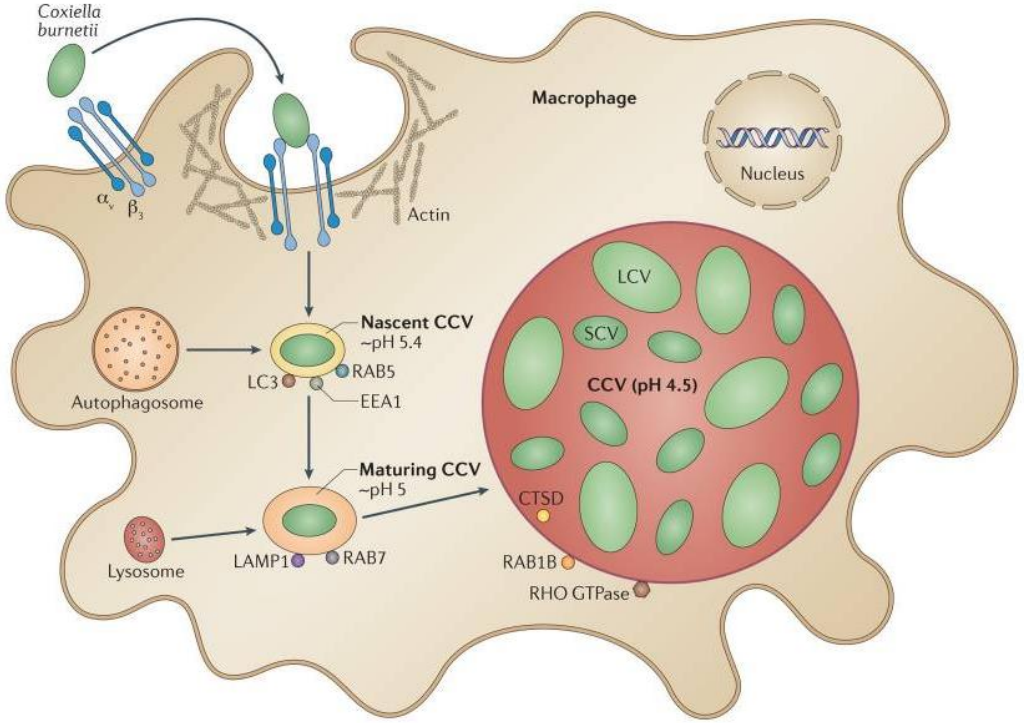
Basic Microbiology

- *Coxiella burnetii* is a short pleomorphic gram-negative rod that is strictly intracellular
- Not easily cultured due to being intracellular
- Can do shell vial technique (Human embryonic lung fibroblasts) to culture but must use Biosafety level 3 containment
- The bacteria multiply within the phagolysosome of macrophages in mammals, using immune evading mechanisms (described on the next slide)

[8]Raoult, Didier. Microbiology and epidemiology of Q fever. UpToDate.

Basic Microbiology

- Biphasic developmental cycle
  - **Small cell variant**: 0.2-0.5 um in size
    - Non-replicating infectious form that is very resistant to environmental stressors
    - Dense cell wall/outer membrane complex
  - **Large cell variant**: >0.5 um in size
    - Replicating phase form that is intracellular
    - More sensitive to environmental stressors
  - After replication, a stationary phase is approached and the number of small cell variants increase before release from host cells

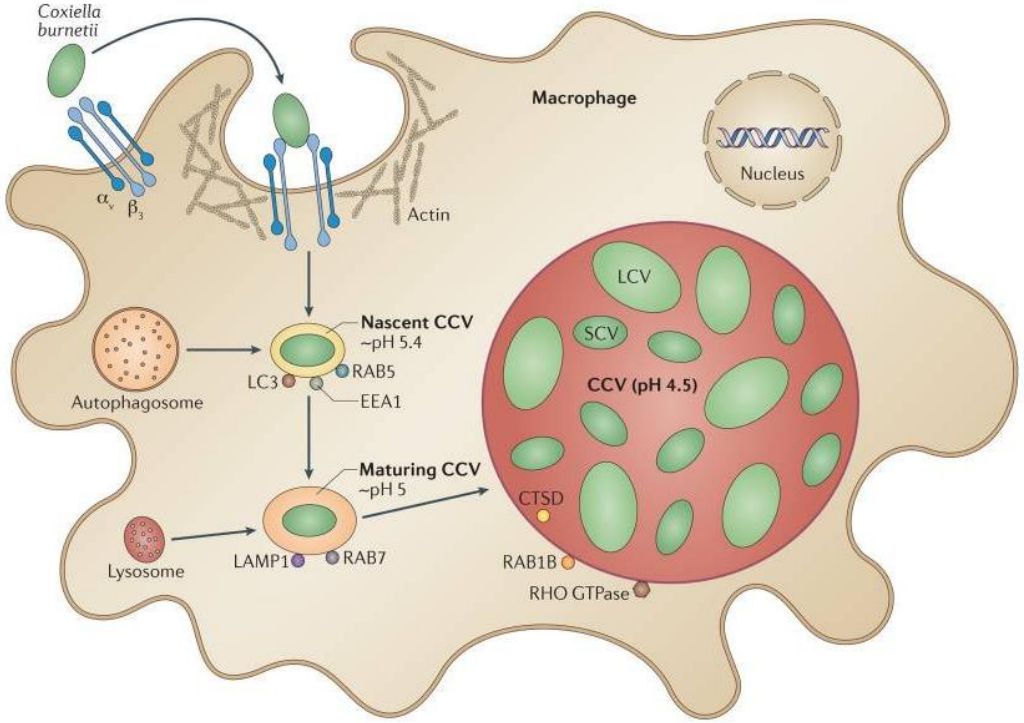


[10]Image from PMID: 23797173

[11]Howe D, Mallavia LP. Coxiella burnetii exhibits morphological change and delays phagolysosomal fusion after internalization by J774A.1 cells.

Basic Microbiology

- In cell culture, we can grow *Coxiella burnetti* and see a change in antigen expression
  - **Phase I antigen expression**: Virulent form with lipopolysaccharide (LPS) having a complete O antigen (blocks the ability of TLR2 to bind)
  - **Phase II antigen expression**: Avirulent form with antigenic shift resulting in a LPS modification which exposes certain proteins on the surface of the bacteria



[10]Image from PMID: 23797173

[10]van Schaik EJ, Chen C, Mertens K, Weber MM, Samuel JE. Molecular pathogenesis of the obligate intracellular bacterium Coxiella burnetii.

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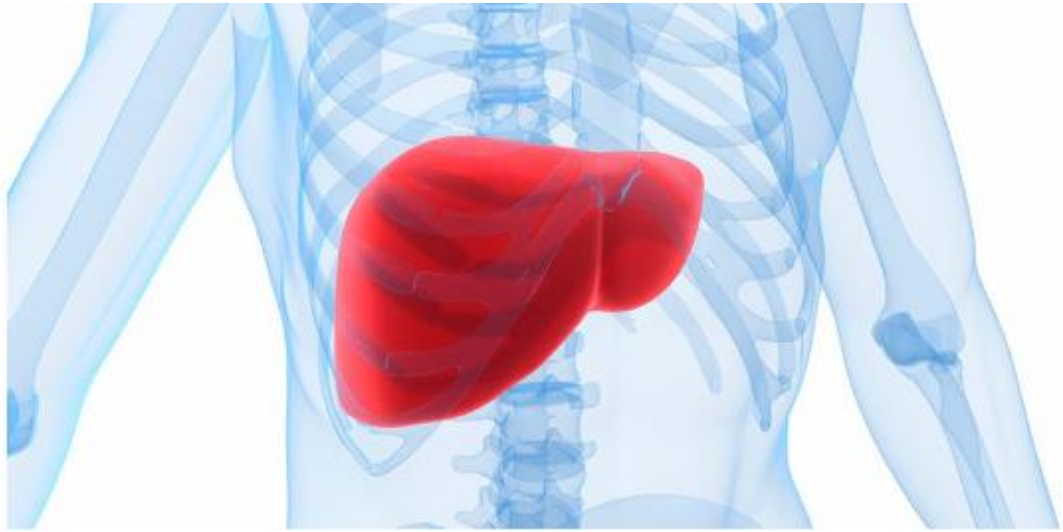


Serology by IFA

- Use phase variation of *Coxiella burnetti* to assess for acute and chronic infections
  - Phase II > Phase I = Acute infection
  - Phase I > Phase II = Chronic infection
- Looking for antibodies (IgM and IgG) to phase I and phase II antigens
  - IgG can be negative early in infections, so IgM is typically ordered

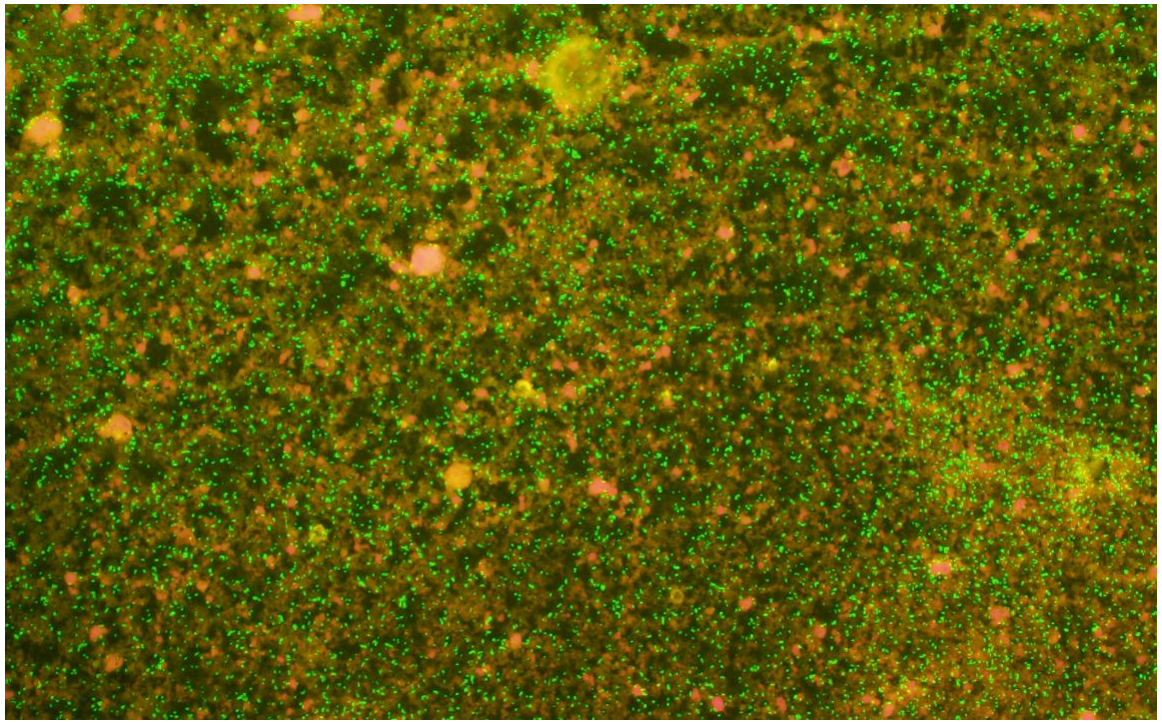
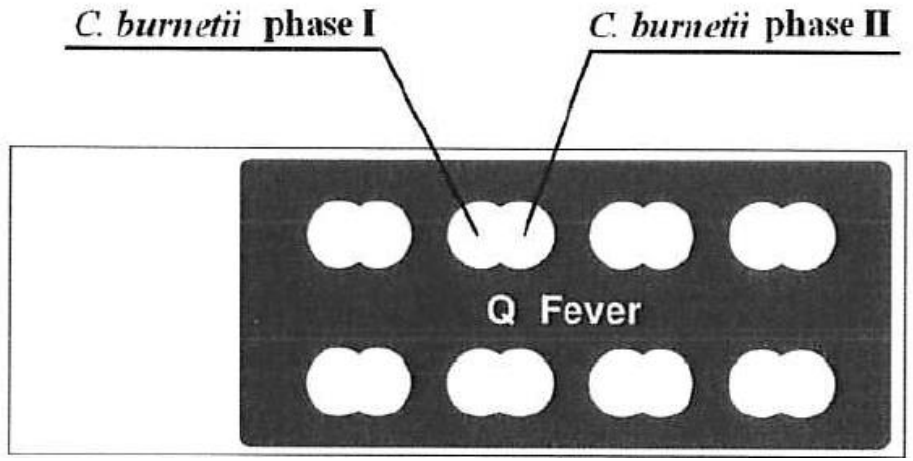
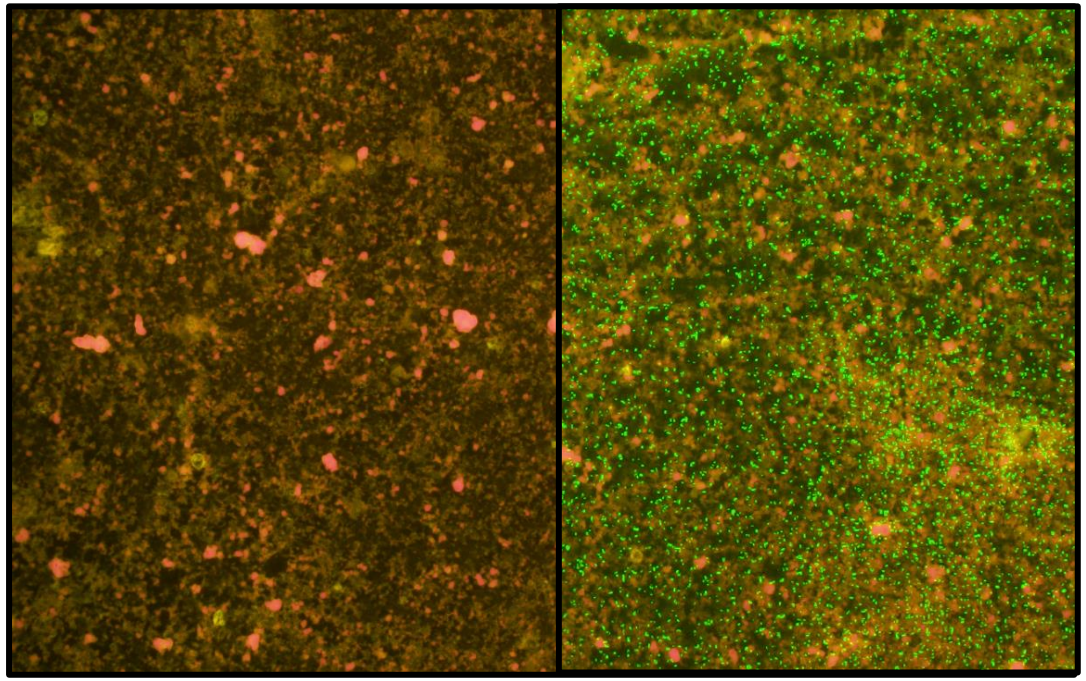


Image courtesy of the Microbial Immunology II lab at ARUP Laboratories

Serology by IFA

- Two-stage sandwich IFA assay
  1. Patient serum is diluted in PBS and added to the slide wells
  2. Fluorescein-labeled anti-IgM/IgG added giving a positive green reaction
- Positive needs the bright fluorescence and correct bacterial morphology
- Screen at 1:16, then titer to endpoint
- Interpretation:
  - **Acute Q fever**: Phase II > Phase I
    - Convalescent sera 4x increase in Phase II IgG
    - Phase II IgG >/= 200, IgM >/= 50
  - **Chronic Q fever**: Phase I IgG > Phase II IgG (usually Phase I IgG >800 and clinical findings)





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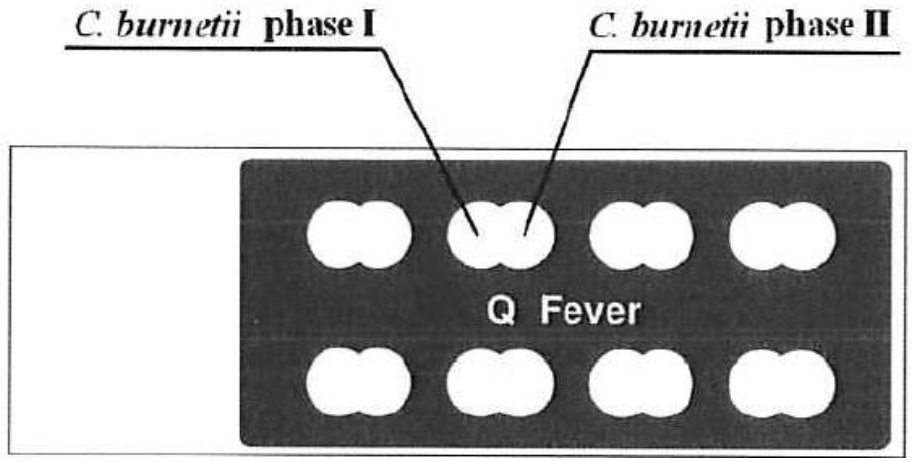


Patient results:

Phase I IgM: Positive, 1:256

Phase I IgG: Positive, 1:512

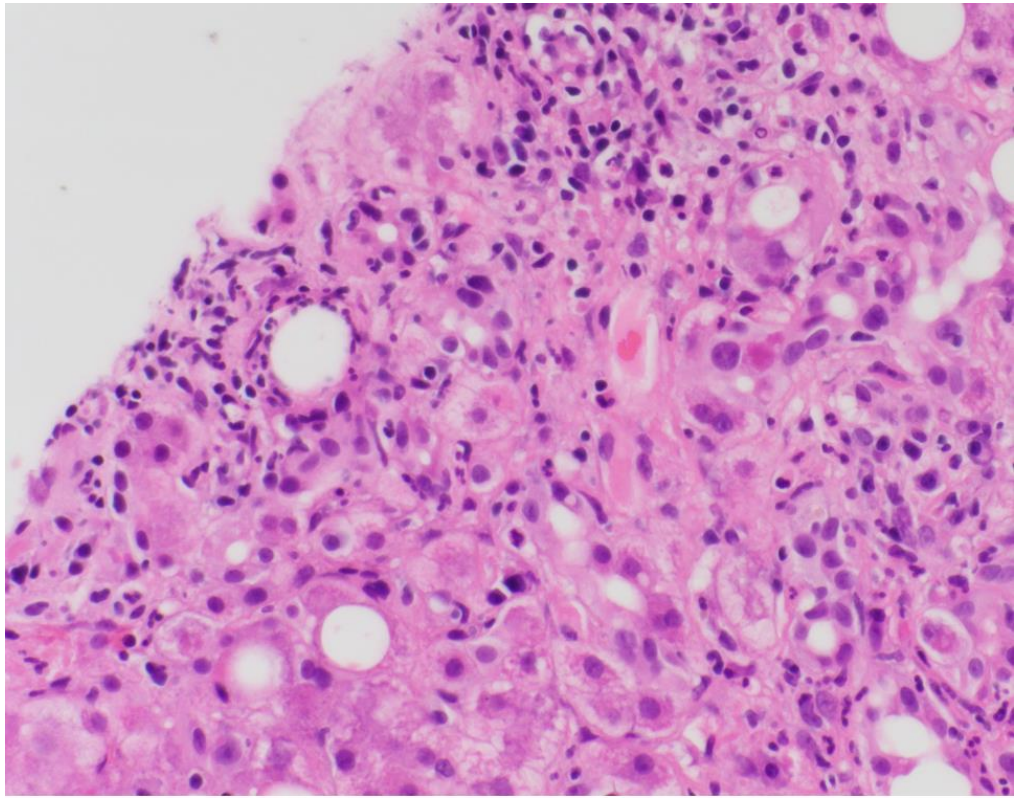
Phase II IgM: Positive, 1:4096

Phase II IgG: Positive, >1:131072

[9]Raoult, Didier. Clinical manifestations and diagnosis of Q fever. UpToDate.

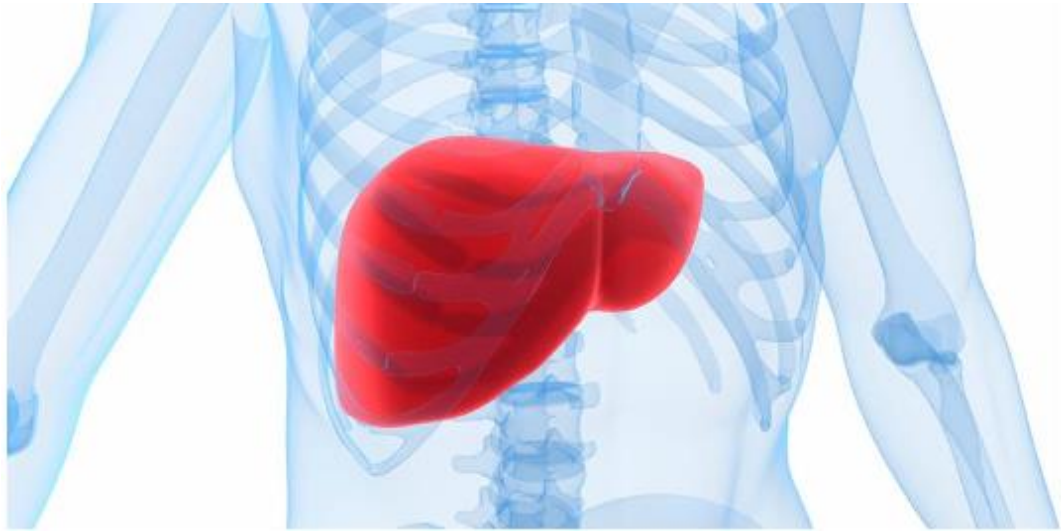
Tissue biopsy

- The fibrin ring granulomas within a tissue specimen are characteristic of *Coxiella* (liver, bone marrow…)
- Ring granulomas can be seen with other etiologies such as viral infections like EBV and CMV



Outline

- Clinical case presentation
- Review of liver anatomy and function
- Laboratory values
- Epstein-Barr Virus
  - Background and clinical features
  - Laboratory testing
- Liver biopsy results
- **Q fever**
  - Introduction and epidemiology
  - Transmission and clinical manifestations
  - Microbiology
  - Laboratory testing
  - **Treatment**
- Summary



Treatment

- Acute Q fever:
  - Asymptomatic patients are not treated
  - Symptomatic patients can receive a short course of Doxycycline (14 days) as first line therapy (other agents include Bactrim or Clarithromycin)
- Special considerations
  - Pregnant women: Can be treated even when asymptomatic with Bactrim
  - High risk groups (valve/vascular disease, antiphospholipid antibodies…) should receive Doxycycline plus Hydroxychloroquine with extended treatment between 12-18 months
- Chronic Q fever: Doxycycline plus Hydroxychloroquine for 18-24 months

[12]Raoult, Didier. Treatment and prevention of Q fever.

Prognosis

- Only 1-5% of patients with Acute Q fever are hospitalized
- Mortality is low with Acute Q fever (self-limited illness)
- Chronic Q fever: the mortality rate can be high

[12]Raoult, Didier. Treatment and prevention of Q fever.

[13]van Roeden SE, Wever PC, Kampschreur LM, et al. Chronic Q fever-related complications and mortality: data from a nationwide cohort.

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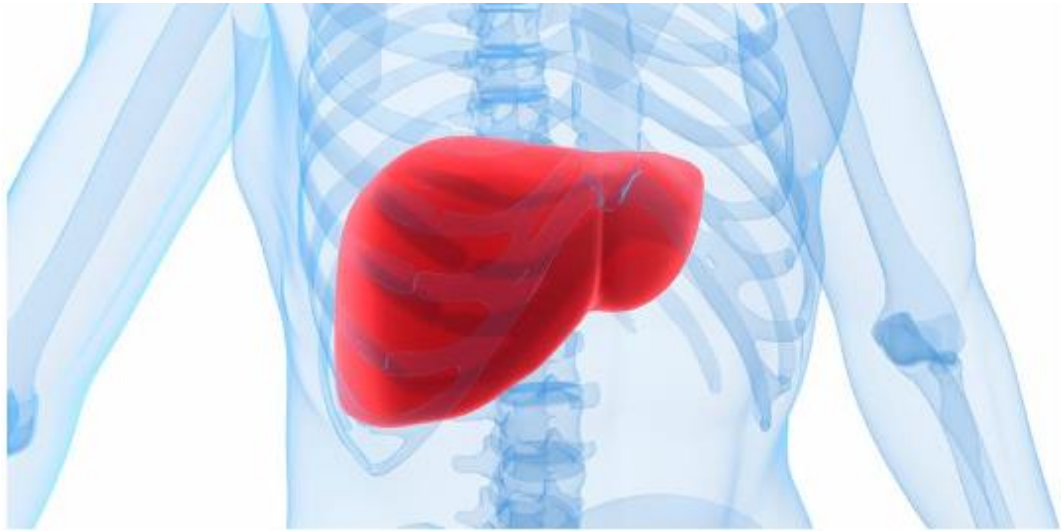

Case Summary

- Patient was diagnosed with Acute Q fever hepatitis and put on Doxycycline for 14 days.
- Repeat serology was performed after 5 months
  - Initial Serology:
    - **Phase I IgM:** Positive, 1:256
    - **Phase I IgG:** Positive, 1:512
    - **Phase II IgM:** Positive, 1:4096
    - **Phase II IgG:** Positive, >1:131072
  - Repeat serology:
    - **Phase I IgG:** Positive, 1:4096
    - **Phase II IgG:** Positive, 1:65,536
- He is asymptomatic so he will continue to be monitored given his rise in Phase I titers.

1. Understand the interpretation of serologic testing for Epstein-Barr Virus

Interpretation of EBV-Specific Serologic Results				
Infection	VCA IgM	VCA IgG	EA	EBNA
No previous	Negative	Negative	Negative	Negative
Acute/primary	Positive	Positive	Positive/negative	Negative
Recent	Positive/negative	Positive	Positive/negative	Positive/negative
Past	Negative	Positive	Negative	Positive
Reactivation[a]	Positive/negative	Positive	Positive	Positive

2. Describe the basic microbiology and transmission of *Coxiella burnetii*

- Q fever is a zoonotic disease caused by the intracellular gram negative bacteria *Coxiella burnetii*
- Individuals that work or live near farm animals are at highest risk for infection through aerosolized forms
- Small cell variant is more infectious and can survive extracellularly
- Large cell variant is the replicating form within the macrophages

3. Explain the serologic testing for Q fever and how we differentiate between acute and chronic infections

- **Acute Q fever**: Phase II > Phase I
  - Convalescent sera 4x increase in Phase II IgG
  - Phase II IgG >/= 200, IgM >/= 50
- **Chronic Q fever**: Phase I IgG > Phase II IgG (usually Phase I IgG >800 and clinical findings)

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