THE YELLOW WAVE

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- AUNA-Oncosalud

ASTMH 2025 Annual Meeting
November 9–13

UNIVERSIDAD PERUANA CAYETANO HEREDIA | Instituto de MEDICINA TROPICAL ALEXANDER VON HUMBOLDT

1

I HAVE NO DISCLOSURES TO MENTION

2

OBJECTIVES

- To recognize the main tropical diseases that present with jaundice
- To review their diagnostic methods
- To examine treatment approaches
- To review preventive measures

3

A BRIEF INTRODUCTION TO JAUNDICE

- Not clinically detectable until serum levels > 2mg/dl
- Best observed at: *ocular conjunctiva, oral mucosa (under the tongue, hard palate)*
- Classification is based on the predominant type of pigment:
  - Unconjugated: overproduction, impaired uptake, abnormal conjugation
  - Conjugated: hepatocellular disease, impaired canalicular excretion, obstruction (intra- or extra-hepatic)

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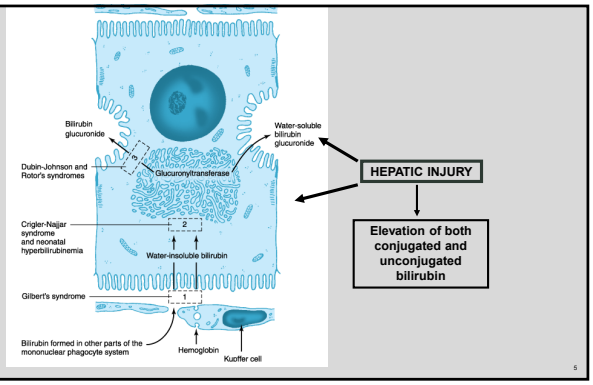

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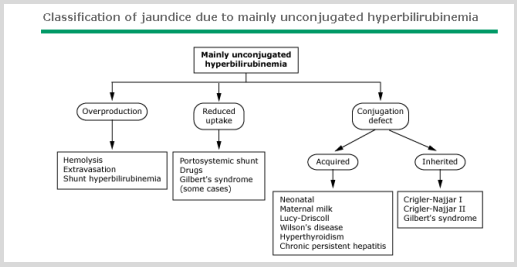
UNCONJUGATED BILIRUBIN



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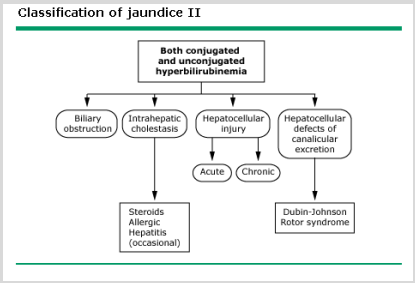
CONJUGATED BILIRUBIN



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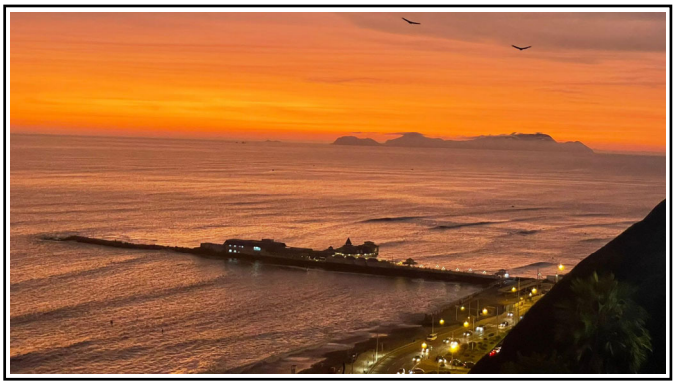

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AGENDA

- A 54-year-old male patient with jaundice out of proportion
- A 47-year-old female patient with sepsis and suspicion of cholangitis, but with no gallstones
- A 19-year-old pregnant with massive hemolysis
- A 32-year-old male with multi-organ failure

9

A 57-YEAR-OLD MALE WITH JAUNDICE OUT OF PROPORTION

- 57-year-old male from Cajamarca (Highlands of north Lima), but lives in Lima
- Six-day history of:
  - Persistent fever (39C); asthenia, generalized myalgia
  - Dark urine and jaundice one day before admission
  - Vomiting and dyspnea on the day of admission
- He works as a mototaxi driver, but complements his income by working in South Lima harvesting grapes in a rural vineyard.
- Exposed to fresh water, mosquito bites, animal contact, and rodents
- PMH; non-relevant

10

PHYSICAL EXAMINATION

- Temperature 38.7C °C, pulse 114, respirations 22, BP 104/76, StHb 95% at FiO2 21%
- Marked jaundice on the sclera
- Facial and lower limb pitting edema
- Chest and CV normal
- Abdomen normal
- CNS normal

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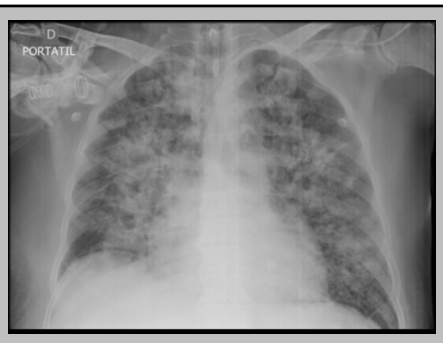
12

LABORATORY TEST RESULTS

- HB 12.7 g/dl; WBC 21,100 (2% bands, 83% PMNs, 3% lymphs); platelets 17,000. cells/ml; INR 1.1
- Creatinine 5.5 mg/dl (<1.1); Urea 199 mg/dl (<40)
- Total bilirubin 25 mg/dl; direct 24.2 mg/dl
- ALT 97 IU/l (<69); AST 83 IU/l (<83)
- Sodium 147 mEq/l; Potassium 6.62 meEq/l; bicarb 12 mEq/l
- C-reactive protein 192; CK 110; negative blood cultures
- HIV; HTLV-1, HVB, HVA, HVC, RPR non-reactive
- Abdominal US; hepatomegaly, no gallstones; common bile duct normal

13



NEXT DAY HE PRESENTED MASSIVE HEMOPTYSIS AND SEVERE RESPIRATORY DISTRESS

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WHAT IS THE MOST LIKELY DIAGNOSIS?

A.Typhoid fever
B. Brucellosis
C. Leptospirosis
D. Yellow fever
E. Pneumonic plague

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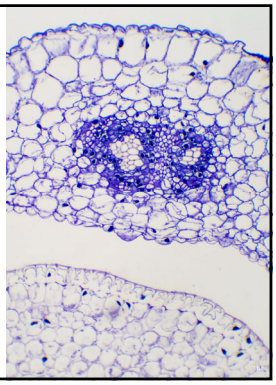
INTRAHEPATIC CHOLESTASIS

- Rare manifestation of infectious diseases
- Mostly bacterial diseases: SEPSIS
  - Leptospirosis (Weil's syndrome)
  - Brucellosis (rare); Q fever
  - Typhoid fever (severe clinical presentation)
  - TBC (milliary dissemination)
  - Pyogenic abscess
  - Rare in amebic liver abscess
- Cholestatic presentation of HAV, HEV, rare CMV, EBV



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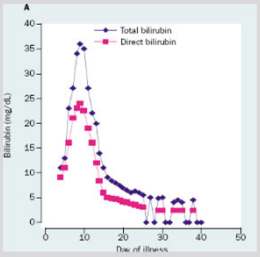
LEPTOSPIROSIS



- icteric form is rare: 5-10%
- bilirubin up to 30-40 mg/dL
- days to weeks to normalize
- ALT < 3xULN
- impairment of ATP-dependent excretion of conjugated bilirubin

Bharti AJ. Lancet Infect Dis 2003;3:757-71.

17

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MAMMAL RESERVOIRS IN ENDEMIC AREAS

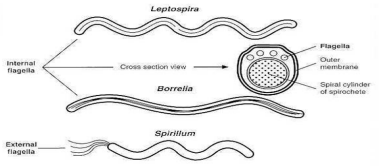
Neotropical opposum, rodents, marsupials and bats infected around the city of Iquitos, Peru

Bharti AR. Lancet Infect Dis 2003;3:757

18

Leptospira interrogans

	Borrelia		
Spirochetes	Treponema	*L. biflexa*	(non-pathogenic)
	Leptospira	***L. interrogans***	**(pathogenic)**



Lepto (Greek): thin
Spira (Latin): coil
Interrogans: shape like?

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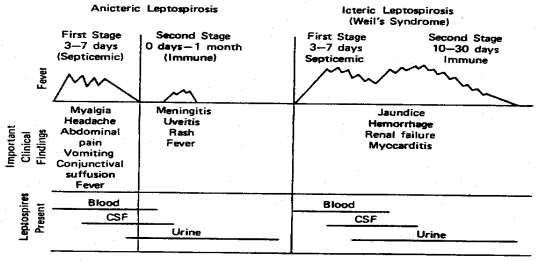
CLINICAL COURSE



Levett PN. J Clin Microbiol 2001;14:296

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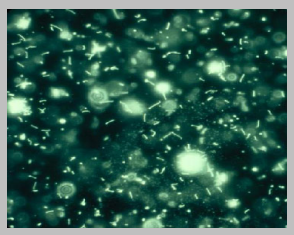
MICROSCOPIC AGGLUTINATION TEST



Baseline MAT 1/400 *L.interrogans icterohaemorrhagiae*

2 weeks later; 1/3200

Courtesy of Andreas Neumayr: Swiss Tropical and Public Health Institute, Basel, Switzerland

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TREATMENT

- Majority of infections are self-limited
- Controversy on the real value of antimicrobials
- Cochrane Systematic Review
  - 9 randomized clinical trials evaluated
  - **insufficient evidence for or against antimicrobial use**
  - use of antibiotics reduced duration of illness by 2-4 days
  - selection of penicillin, ceftriaxone or doxycycline does not seem to impact mortality nor duration of fever
- Supportive management and antibiotic use

Cochrane Database Syst Rev. 2024 Mar 14;3(3):CD014960.

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TREATMENT

- Ceftriaxone 1-2g, 1x/d, iv for 7 days (children: 25-50mg/kg 1x/d)
- Penicillin G 1-2 MU, 6x/d, iv for 7 days
- Doxycycline 100mg, bid, po for 7 days
- Azithromycin 500mg, 1xd, po for 3 days
- Streptomycin 1-2g, 1-2xd, im for 2-4 days

	First line	Alternative
Severe disease	Ceftriaxone PNC	doxycycline, STM
Mild to moderate	**doxycycline** **amoxicillin**	**azithromycin,**

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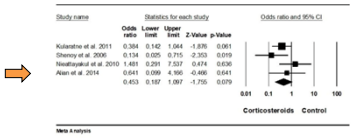
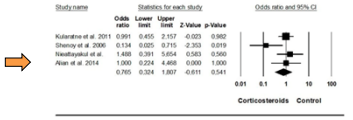
Mortality



Effect of corticosteroids on need for mechanical ventilation



ROLE OF STEROIDS

1. No effect on mortality
2. No effect on the need for mechanical ventilation
3. No effect on LOS
4. No effect on Jarisch-Herxheimer

J Clin Med. 2024;13(15):4310
Database of Systematic Reviews 2025, Issue 7.

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In 1886, Weil described an acute infectious disease, characterized by fever and jaundice..... it has not been definitely determined whether it is a specific disease or only jaundice which may be due to various causes

THE PRINCIPLES AND PRACTICE OF MEDICINE

WILLIAM OSLER

1892

25

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A 47-YEAR-OLD FEMALE WITH SEPSIS AND SUSPICION OF CHOLANGITIS

- 47-year-old female from Abancay (Highlands of eastern Peru), but lives in Cuzco
- Two-week history of:
  - Severe right upper quadrant pain
  - Dark urine and jaundice one week before admission
  - Vomiting and fever the day of admission
- Housewife; lives on a rural farm
- Exposed to fresh water, animal contact, and eats all sorts of vegetables
- PMH; non-relevant

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PHYSICAL EXAMINATION

- Temperature 38.7C °C, pulse 98, respirations 18, BP 89/72, StHb 97% at FiO2 21%
- Marked jaundice on the sclera
- Chest and CV normal
- Severe pain on palpation at the right upper quadrant
- No peritoneal signs

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LABORATORY TEST RESULTS

- HB 14.7 g/dl; WBC 18,100 (4% bands, 83% PMNs, 8% lymphs, 5% eos); platelets 467,000. cells/ml; INR 1.1
- Creatinine8.18 mg/dl (<1.1); Urea 41 mg/dl (<40)
- Total bilirubin 12 mg/dl; direct 9.2 mg/dl, AlkP 5 times UNL
- ALT 90 IU/l (<69); AST 67 IU/l (<83)
- Sodium 147 mEq/l; Potassium 4.62 meEq/l
- C-reactive protein 216; blood cultures +ve for pan-susceptible *E. coli*
- HIV; HTLV-1, HVB, HVA, HVC, RPR non-reactive
- Abdominal US; hepatomegaly, no gallstones; dilated common bile duct with a filling defect confirmed at an MRI cholangiogram

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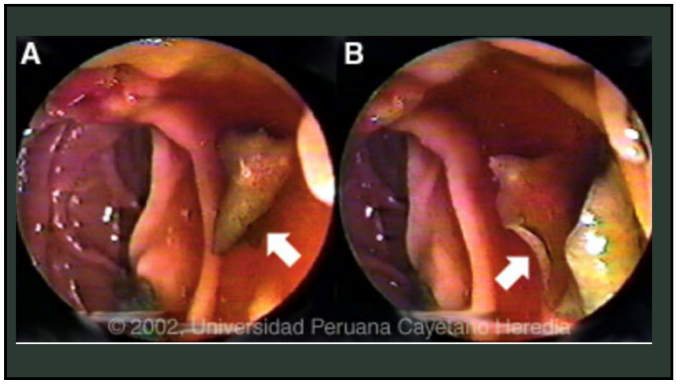

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WHAT IS THE MOST LIKELY DIAGNOSIS?

A. Ascariasis
B. Fascioliasis
C. Paragonimiasis
D. Teniasis
E. Strongyloidiasis

31

EXTRA HEPATIC CHOLESTASIS

- Primarily associated with gallstones or biliary-pancreatic cancer
- Parasites can obstruct the main duct:
  - *Ascaris lumbricoides*
  - *Fasciola hepatica*
  - Asian trematodes: Opisthorchis and Clonorchis
  - *Tenia solium* (very rare, few reports)
- Cholangiopathy associated with coccidian parasites in HIV patients
- Extrinsic compression of the biliary tract by a hydatid cyst

Gastroenterol Clin North Am. 2020 Jun;49(2):379-410.

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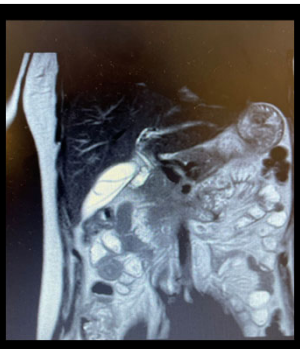

Ascaris lumbricoides

Courtesy of Dr Carolina de la Flor

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Hydatid cyst broken to the common biliary tract

Courtesy of Dr Karen Luhman and Pedro Legua

Gorgas Case of the week 2017-11

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FASCIOLIASIS

- Zoonosis of worldwide distribution
- Complex life cycle
- Acute or invasive phase; chronic, mostly asymptomatic phase
- Complications associated with both phases of illness
- Life span: 9-13 years
- Serology for acute phase; FAS2-ELISA; Egg detection-chronic phase
- Triclabendazole; 10 mg/kg/d per 1-2 days (failures reported)

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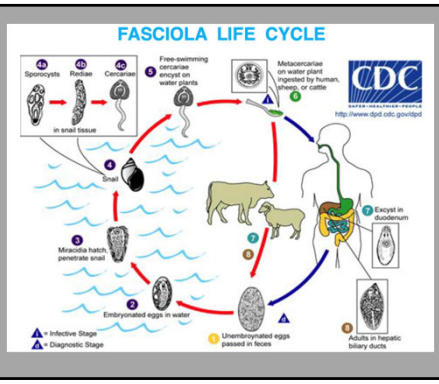

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COURTESY OF DR PEDRO LEGUA

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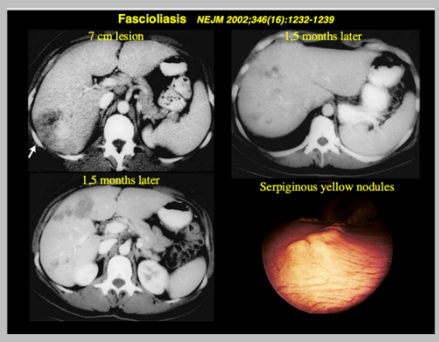

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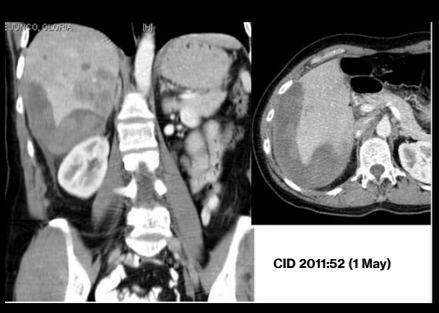

CID 2011:52 (1 May)

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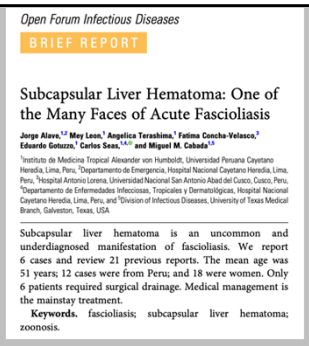

Open Forum Infectious Diseases

BRIEF REPORT

Subcapsular Liver Hematoma: One of the Many Faces of Acute Fascioliasis

Jorge Alave,[1,2] Mey Leon,[1] Angelica Terashima,[1] Fatima Concha-Velasco,[3] Eduardo Gotuzzo,[1] Carlos Seas,[1,4,5] and Miguel M. Cabada[1,5]

[1]Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru, [2]Departamento de Emergencia, Hospital Nacional Cayetano Heredia, Lima, Peru, [3]Hospital Antonio Lorena, Universidad Nacional San Antonio Abad del Cusco, Cusco, Peru, [4]Departamento de Enfermedades Infecciosas, Tropicales y Dermatológicas, Hospital Nacional Cayetano Heredia, Lima, Peru, and [5]Division of Infectious Diseases, University of Texas Medical Branch, Galveston, Texas, USA

Subcapsular liver hematoma is an uncommon and underdiagnosed manifestation of fascioliasis. We report 6 cases and review 21 previous reports. The mean age was 51 years; 12 cases were from Peru; and 18 were women. Only 6 patients required surgical drainage. Medical management is the mainstay treatment.

Keywords. fascioliasis; subcapsular liver hematoma; zoonosis.

Open Forum Infect Dis. 2024 Sep 23;11(10):ofae554

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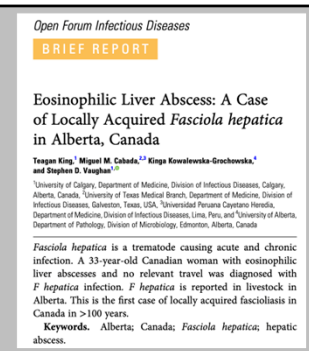

Open Forum Infectious Diseases

BRIEF REPORT

Eosinophilic Liver Abscess: A Case of Locally Acquired *Fasciola hepatica* in Alberta, Canada

Teagan King,[1] Miguel M. Cabada,[2,3] Kinga Kowalewska-Grochowska,[4] and Stephen D. Vaughan[1,5]

[1]University of Calgary, Department of Medicine, Division of Infectious Diseases, Calgary, Alberta, Canada, [2]University of Texas Medical Branch, Department of Medicine, Division of Infectious Diseases, Galveston, Texas, USA, [3]Universidad Peruana Cayetano Heredia, Department of Medicine, Division of Infectious Diseases, Lima, Peru, and [4]University of Alberta, Department of Pathology, Division of Microbiology, Edmonton, Alberta, Canada

Fasciola hepatica is a trematode causing acute and chronic infection. A 33-year-old Canadian woman with eosinophilic liver abscesses and no relevant travel was diagnosed with *F hepatica* infection. *F hepatica* is reported in livestock in Alberta. This is the first case of locally acquired fascioliasis in Canada in >100 years.

Keywords. Alberta; Canada; *Fasciola hepatica*; hepatic abscess.

Open Forum Infect Dis. 2024 Feb 19;11(3):ofae101

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The liver flukes occupy the bile passages and the upper portion of the small intestine. When in large numbers, they may cause serious and fatal disease of the liver, usually with ascites and jaundice

THE PRINCIPLES AND PRACTICE OF MEDICINE

WILLIAM OSLER

1892

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A 19-YEAR-OLD PREGNANT WITH MASSIVE HEMOLYSIS

A 19-year-old pregnant woman (22 weeks) presents with a three-day history of fever and jaundice:

- Headache, myalgia, and jaundice
- Evaluated in a peripheral health care center. Noticed fetal loss, marked jaundice, and confusion. Transferred to a Regional Hospital in the highlands of Huaraz.
- Transferred to Lima due to a critical condition.

PMH non-relevant. Lives at an altitude of 2350 masl; farmer

44

45

PHYSICAL EXAMINATION

- T 37.4 ºC, R 22, HR 115, BP 82/48, Sat O2 90%
- Skin: marked jaundice.
- Lungs: Rales in both lungs.
- CV: Taquicardic; no murmurs.
- Abdomen: non-painful hepatomegaly (spam 20 cm).
- CNS: Glasgow 14; confusion. No meningeal signs.
- Vaginal bleeding.

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LABORATORY TEST RESULTS

	On admission
Hematocrit, retics	20%; 8%
WBC	20700 (2B, 80 N, 1 Eos, 4 Mo,13 L)
Platelets	70 000
Bilirrubin conj/ unconj	3,9 / 13,1 mg/dl
ALT/AST	100/27 [59/72 IU/L]
Alk Phospatase	150 mg/dl [100-140 mg/dl]
INR	1.56
Glucose	80 mg/dl [90-110mg/dL]
HIV ELISA; HTLV-1; VDRL	Non-reactive

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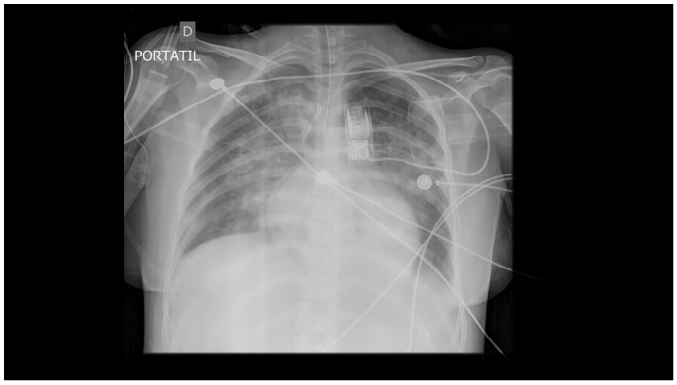

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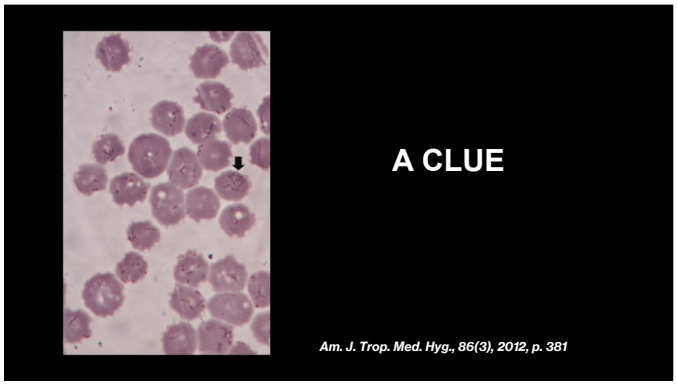

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WHAT IS THE MOST LIKELY DIAGNOSIS?

A. Malaria
B. Babesiosis
C. Bartonellosis
D. American trypanosomiasis
E. Loxoscelism

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INTRAVASCULAR HEMOLYSIS

- Few infectious diseases cause intravascular hemolysis.
- It has been reported in:
  - Malaria: *P. falciparum* >>>> other species
  - Babesiosis
  - Bartonellosis by *B. bacilliformis, B. rochalimae*
  - Sepsis by *Clostridium perfringens*
  - Snake and spider bites: *Bothrops, Lachesis,* and *Loxosceles*
- Many pathogens cause hemolytic anemia:
  - Viruses: CMV, EBV, HBV, HCV, parvovirus B19, HIV, coxsackie
  - Bacteria: *Leptospira, M. tuberculosis, Campylobacter, Shigella, Mycoplasma, Haemophilus influenzae* type b.
  - Fungi: *Aspergillus*

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CARRION'S DISEASE: A BRIEF HISTORY

- The highest railroad (Lima-La Oroya 4818 masl) was built 1870-1880
- 7000 railroad workers died
- People living in these areas had verrucous skin lesions
- A Peruvian medical student, Daniel Carrion, self-inoculated the fluid from a verrucous lesion and acquired the acute phase
- Died on October 5, 1885
- Alberto Barton discovered the germ in 1900

Am J Trop Med Hyg 1968:17:503

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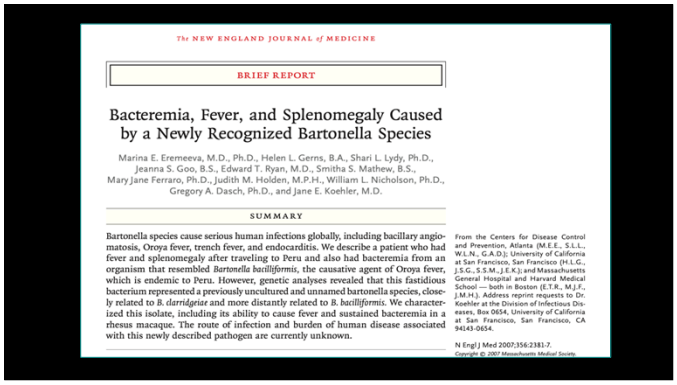
ACUTE SOUTH AMERICAN BARTONELLOSIS

Restricted to Andean valleys of Peru and Colombia-Ecuador
Very few cases among travelers
Vector-borne transmitted disease; Lutzomyia sp.
Bartonella bacilliformis; B. ancashensis; B. rochalimae
Severe hemolytic anemia followed by transient cellular immunosuppression
High index of suspicion; microscopy; quick treatment (ciprofloxacin+ceftriaxone)

54



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Bacteremia, Fever, and Splenomegaly Caused by a Newly Recognized Bartonella Species

Marina E. Eremeeva, M.D., Ph.D., Helen L. Gerns, B.A., Shari L. Lydy, Ph.D., Jeanna S. Goo, B.S., Edward T. Ryan, M.D., Smitha S. Mathew, B.S., Mary Jane Ferraro, Ph.D., Judith M. Holden, M.P.H., William L. Nicholson, Ph.D., Gregory A. Dasch, Ph.D., and Jane E. Koehler, M.D.

SUMMARY

Bartonella species cause serious human infections globally, including bacillary angiomatosis, Oroya fever, trench fever, and endocarditis. We describe a patient who had fever and splenomegaly after traveling to Peru and also had bacteremia from an organism that resembled *Bartonella bacilliformis*, the causative agent of Oroya fever, which is endemic to Peru. However, genetic analyses revealed that this fastidious bacterium represented a previously uncultured and unnamed bartonella species, closely related to *B. clarridgeiae* and more distantly related to *B. bacilliformis*. We characterized this isolate, including its ability to cause fever and sustained bacteremia in a rhesus macaque. The route of infection and burden of human disease associated with this newly described pathogen are currently unknown.

From the Centers for Disease Control and Prevention, Atlanta (M.E.E., S.L.L., W.L.N., G.A.D.); University of California at San Francisco, San Francisco (H.L.G., J.S.G., S.S.M., J.E.K.); and Massachusetts General Hospital and Harvard Medical School — both in Boston (E.T.R., M.J.F., J.M.H.). Address reprint requests to Dr. Koehler at the Division of Infectious Diseases, Box 0654, University of California at San Francisco, San Francisco, CA 94143-0654.

N Engl J Med 2007;356:2381-7.

55

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A 32-YEAR-OLD MALE WITH MULTI ORGAN FAILURE

41 yo male presenting with acute onset of fever, encephalopathy and jaundice one day after returning from a vacation trip to the jungle of Peru

- 5 dba: fever, headache, muscle pain in the lower extremities, and diffuse abdominal pain
- 4 dba: nausea and vomiting; received IV fluids and antibiotics at another hospital
- 1 dba: oliguria, jaundice, and altered mental status

Transferred to our ER for dialysis support

57

Born in Cuzco, lives in Lima

PMHx: Childhood asthma

Vaccines: Hepatitis B, no pre-travel advice

Allergies: none

Travel history: jungle of San Martin (for 2 days), then to the jungle of Loreto (near Contamana city for 11 days); stayed on farms, used bed nets at night.

Sexually active, monogamous.

58

PHYSICAL EXAMINATION

- T 36.5 °C, R 34, HR 122, BP 150/89
- Acutely ill, marked acidotic respiration
- Dehydrated (capillary refill > 2 seconds); jaundice; spontaneous mucosal bleeding (oral, nose, rectal), spontaneous bleeding in venipuncture sites and at the CVC insertion site
- Abdomen: distended, normal bowel sounds. No visceromegaly.
- Lethargic; no focal or meningeal signs

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LABORATORY RESULTS

	On admission
Hematocrit	44%
WBC	9050 (58 N, 0 Eos, 12 Mo, 30 L)
Platelets	188000
ALT/AST	13200/11253 [59/72 IU/L]
PT	71.3 [N<13]
Albumin	3.3 g/L [3.5-5 g/dL]
Glucose	77 mg/dl [90-110 mg/dL]
Creatinine	8.3 mg/dl
LDH	Extremely high (not measurable
Urine	Proteins: 500 mg/dl RBC : 95 /hpf

pH 7.3; HCO3, 3.1;
Serum lactate 7.3

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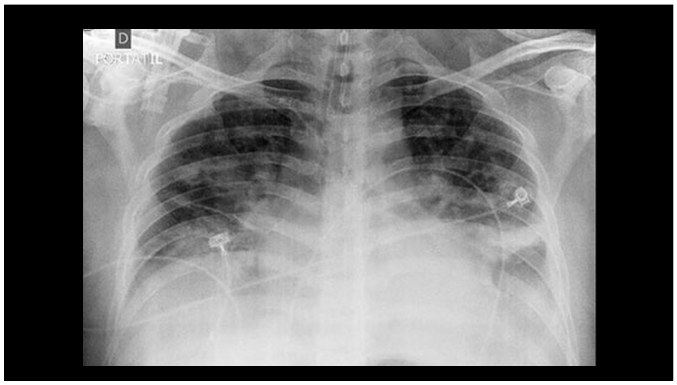

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WHAT IS THE MOST LIKELY DIAGNOSIS?

A. Delta hepatitis
B. Hepatitis E
C. Hemorrhagic dengue
D. Weil's syndrome
E. Yellow fever

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HEPATOCELLULAR INJURY

- More commonly caused by viral infections.
- Fever, bleeding, jaundice, and renal failure, MOF:
  - YF: multiorgan failure, severe hepatocellular damage, proteinuria
  - Dengue: liver involvement is rare, no proteinuria; arthralgia, myalgia, rash, leukopenia, thrombocytopenia
  - HBV: renal disease and proteinuria are not common
  - Other VHFs: geographic distribution (Junin, Guanarito, Mapuche)
  - Leptospirosis: no hepatocellular injury
- Also seen in prolonged shock: sepsis, cholera

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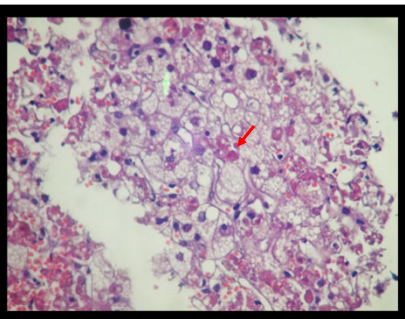

Post-morten liver sample (HE): Councilman bodies (red arrow), microvesicular esteatosis and necrosis with minimal inflammatory response

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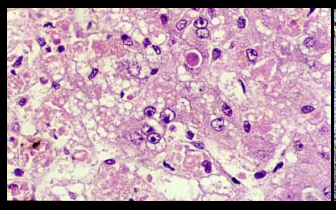

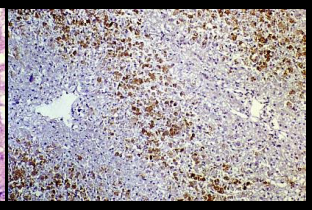

HE stain and immunoperoxidase: mild inflammatory reaction, mid-zonal necrosis, mid zonal fatty changes, Councilman bodies (apoptotic liver cells, eosinophilic bodies)

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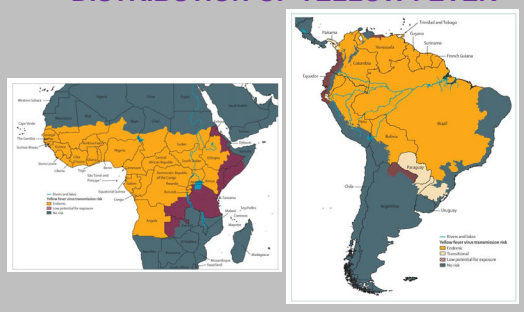
DISTRIBUTION OF YELLOW FEVER



http://www.cdc.gov/yellowfever/maps/

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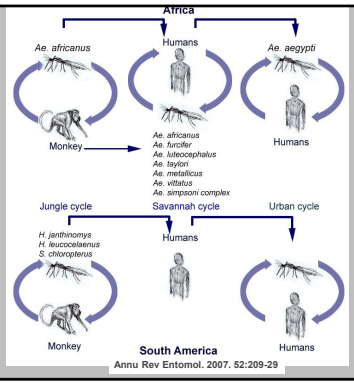

Annu Rev Entomol. 2007. 52:209-29

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CLINICAL PRESENTATION

Three-stage clinical illness:

- **Period of infection:** 3-4 days; similar to any viral infection
- **Period of remission:** 2 days after the infection period; only about 15 % of patients develop the third stage
- **Period of intoxication:** 3-6 days after infection; fever returns with worsening of symptoms and multiorgan failure

Differential diagnosis: leptospirosis, malaria, severe dengue, rickettsial diseases, fulminant viral hepatitis, other viral hemorrhagic fevers (Junin, Guanarito, Machupo, Sabia, Lassa, Ebola, Rift Valley fever)

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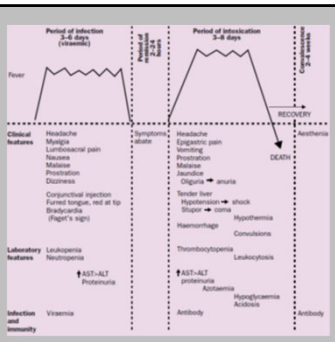

Lancet Infect Dis 2001;1:11-20.

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DIAGNOSIS

- **Serology:**
  - Ig M antibodies by ELISA.
  - Rising titers in paired sera are confirmatory.
  - Cross reaction with other flaviviruses
- **Detection of viral genome** (first five days of illness)
- **Histopathology on post-mortem liver samples**:
  - Mid-zonal necrosis
  - Eosinophilic degeneration of hepatocytes (Councilman bodies).
  - Presence of microvesicular fatty changes
  - Minimal inflammatory response

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TREATMENT- PREVENTION

- Peru reports the highest number of cases in the region
- No effective antiviral therapy is available
- Supportive treatment (dialysis, hemodynamic and ventilator support) when indicated
- Prevention with live attenuated vaccine (17D-204 and 17 DD); produces high levels of life-long protection.
- Targeted populations for vaccination: >9 months of age who are traveling to or living in high-risk areas with a booster every 10 years (?)

Am J Trop Med Hyg 2013; 89:434

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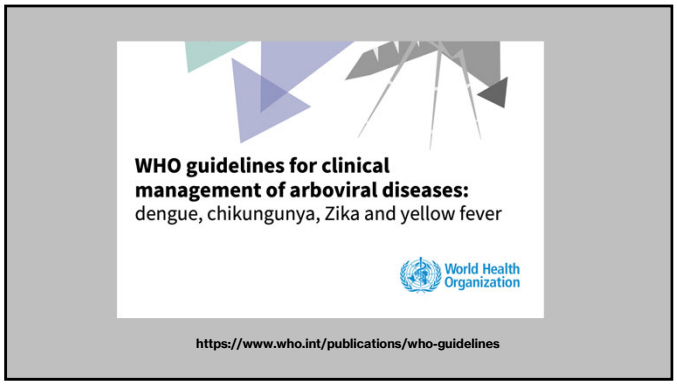

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An acute febrile disease of tropical and subtropical countries, characterized by jaundice and hemorrhages, and due to the action of a specific virus, the nature of which is yet unknown

THE PRINCIPLES AND PRACTICE OF MEDICINE

WILLIAM OSLER

1892

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