Identification and Care of Patients with Hantavirus Disease

Clinician Outreach and Communication Activity (COCA) Call

June 30, 2016

Office of Public Health Preparedness and Response

Division of Emergency Operations

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- **Using the Webinar System**
  - “Click” the Q&A tab at the top left of the webinar tool bar
  - “Click” in the white space
  - “Type” your question
  - “Click” ask

- **On the Phone**
  - Press Star (*) 1 to enter the queue
  - State your name
  - Listen for the operator to call your name
  - State your organization and then ask your question

Objectives

At the conclusion of this session, the participant will be able to:

- **Describe the risk factors, endemic areas, and incubation period of hantavirus infection**
- **Identify the clinical presentation and methods to identify a patient with hantavirus in the clinical setting**
- **Understand the parameters of clinical management and critical care for patients with hantavirus**

Today's First Presenter

Barbara Knust, DVM, MPH, DCAVPM
Epidemiologist
Office of Infectious Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Today's Second Presenter

Gregory Mertz, MD
Professor Emeritus
Department of Internal Medicine
University of New Mexico

Today's Third Presenter

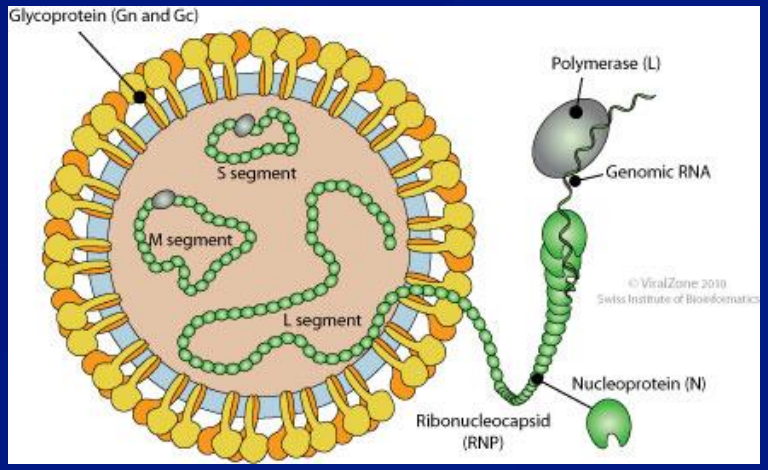
Michelle Harkins, MD
Associate Professor of Medicine
Division Chief, Pulmonary, Critical Care, and Sleep Medicine
Department of Internal Medicine
University of New Mexico

Hantavirus Overview and Epidemiology

- Hantavirus global overview
- US Epi summary
- Diagnostics
- Hantavirus surveillance in the US

Hantaviruses

- *Bunyavirus* family
- Primarily rodent reservoirs
- Human infection
  - Inhalation of excreta
  - Bites possible

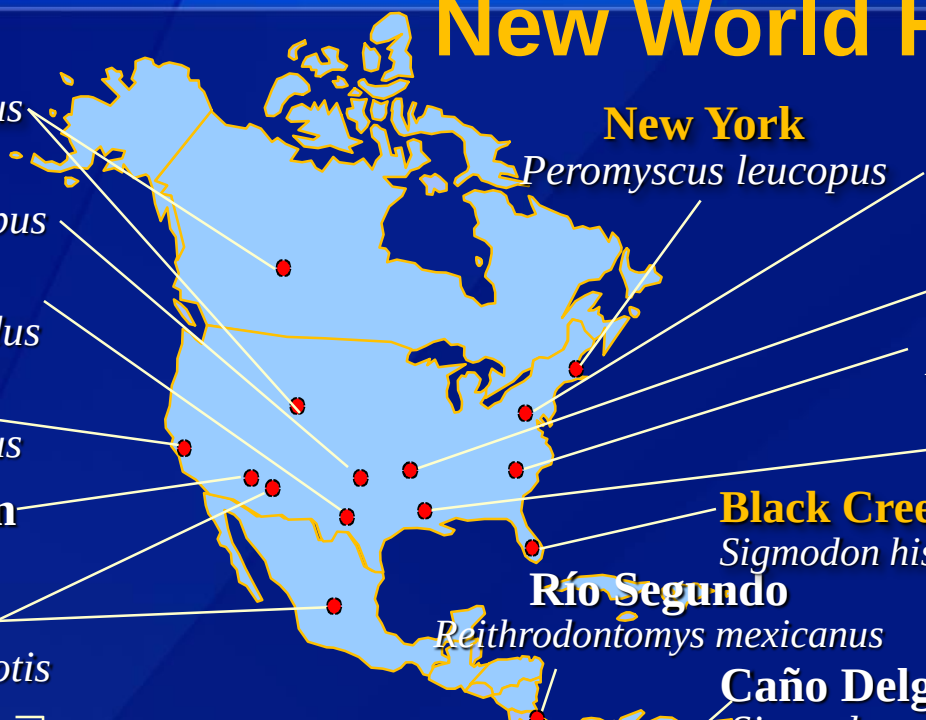


- Hemorrhagic fever with renal syndrome (HFRS)
  - Old-world hantaviruses (Seoul virus likely throughout world)
  - Europe and Asia

- Hantavirus pulmonary syndrome (HPS)
  - New-world hantaviruses
  - Numerous pathogenic hantavirus species across North and South America

Image credit: Viral Zone

New World Hantaviruses



Sin Nombre
Peromyscus maniculatus

Blue River
Peromyscus leucopus

Muleshoe
Sigmodon hispidus

Isla Vista
Microtus californicus

Limestone Canyon
Peromyscus boylii

El Moro Canyon
Reithrodontomys megalotis

Calabazo
Zygodontomys brevicauda

Choclo
Oligoryzomys fulvescens

Río Mearim
Holochilus sciureus

Anajatuba
Oligoryzomys formesi

Bermejo
Oligoryzomys chacoensis

Orán
Oligoryzomys longicaudatus

New York
Peromyscus leucopus

Prospect Hill
Microtus pennsylvanicus

Bloodland Lake
Microtus ochrogaster

Monongahela
Peromyscus maniculatus

Bayou
Oryzomys palustris

Black Creek Canal
Sigmodon hispidus

Río Segundo
Reithrodontomys mexicanus

Caño Delgadito
Sigmodon alstoni

Río Mamoré
Oligoryzomys microtis

Andes
Oligoryzomys longicaudatus

Castelo dos Sonhos
Oligoryzomys eliurus

Laguna Negra
Calomys laucha

Juquitiba
Oligoryzomys nigripes

Araraquara
Necromys lasiuris

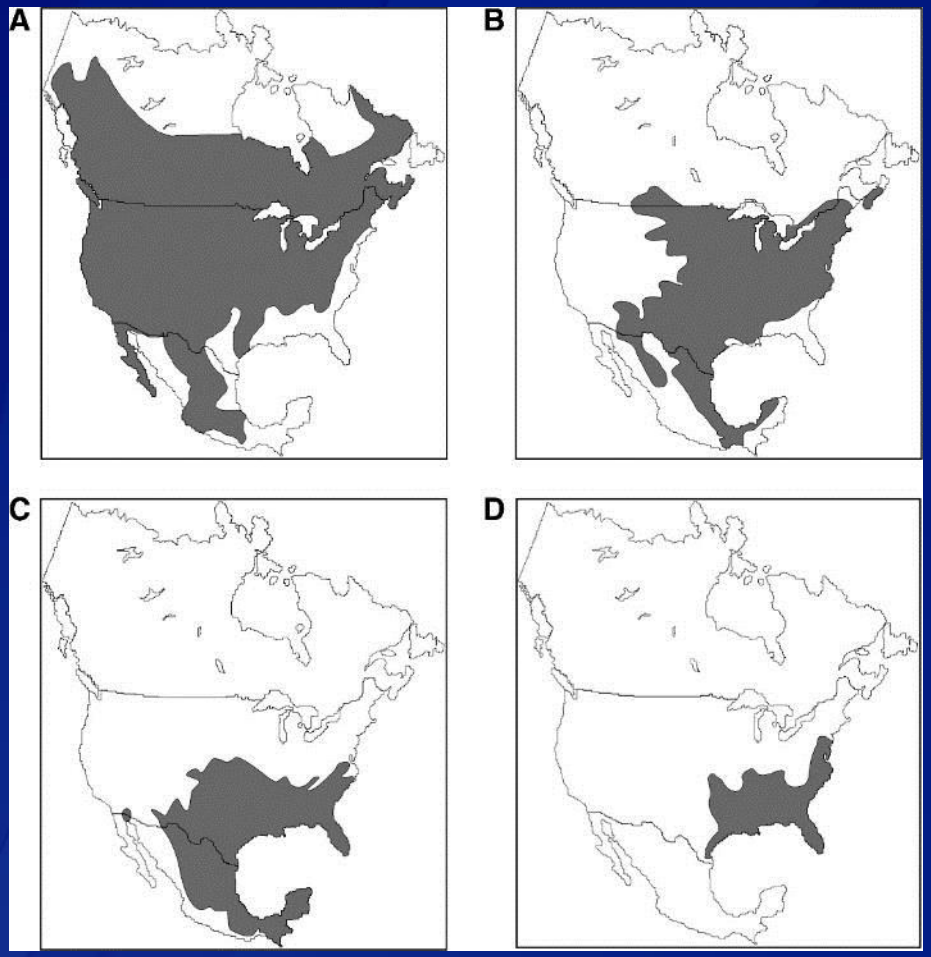
Central Plata
Oligoryzomys flavescens

Maciel
Necromys benefactus

Hu39694
Unknown Host

Lechiguanas
Oligoryzomys flavescens

Rodent Reservoirs of Pathogenic Hantaviruses in the US



A. Deer mouse (Sin Nombre virus)
B. White-footed mouse (New York virus)
C. Hispid cotton rat (Black Creek Canal virus)
D. Rice rat (Bayou virus)

From: Mills et al, *Vector-Borne and Zoonotic Diseases* 2009

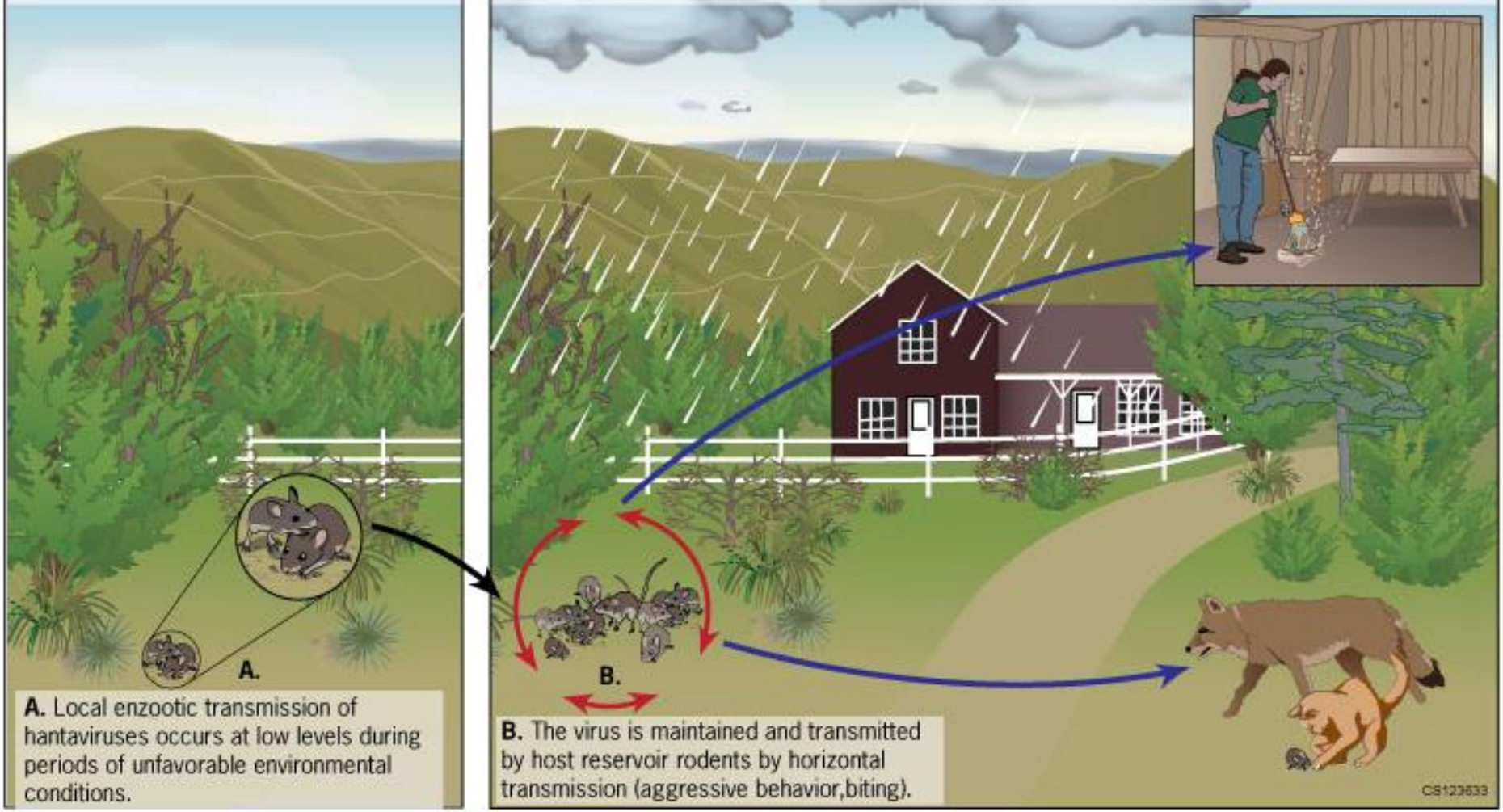
Hanta Virus Ecology

Enzootic Cycle

Many hantaviruses are known to cause hantavirus pulmonary syndrome (HPS). Each virus has a single primary host. The most important hantavirus in the US in the Sin Nombre virus, hosted by the deer mouse.

Epizootic Cycle

Favorable environmental conditions such as mild winters and summer rainfall may cause dramatic increases in rodent populations. More rodents become infected under crowded conditions. Deer mice may enter human structures in rural areas. Humans may become infected when they inhale airborne virus or come into direct contact with infected rodents or their urine, feces, or nests. Other mammal species (cats, dogs, coyotes) may be infected through contact with rodent hosts, but they are not known to transmit the virus.



A. Local enzootic transmission of hantaviruses occurs at low levels during periods of unfavorable environmental conditions.

B. The virus is maintained and transmitted by host reservoir rodents by horizontal transmission (aggressive behavior,biting).

Hantavirus Pulmonary Syndrome Epidemiology

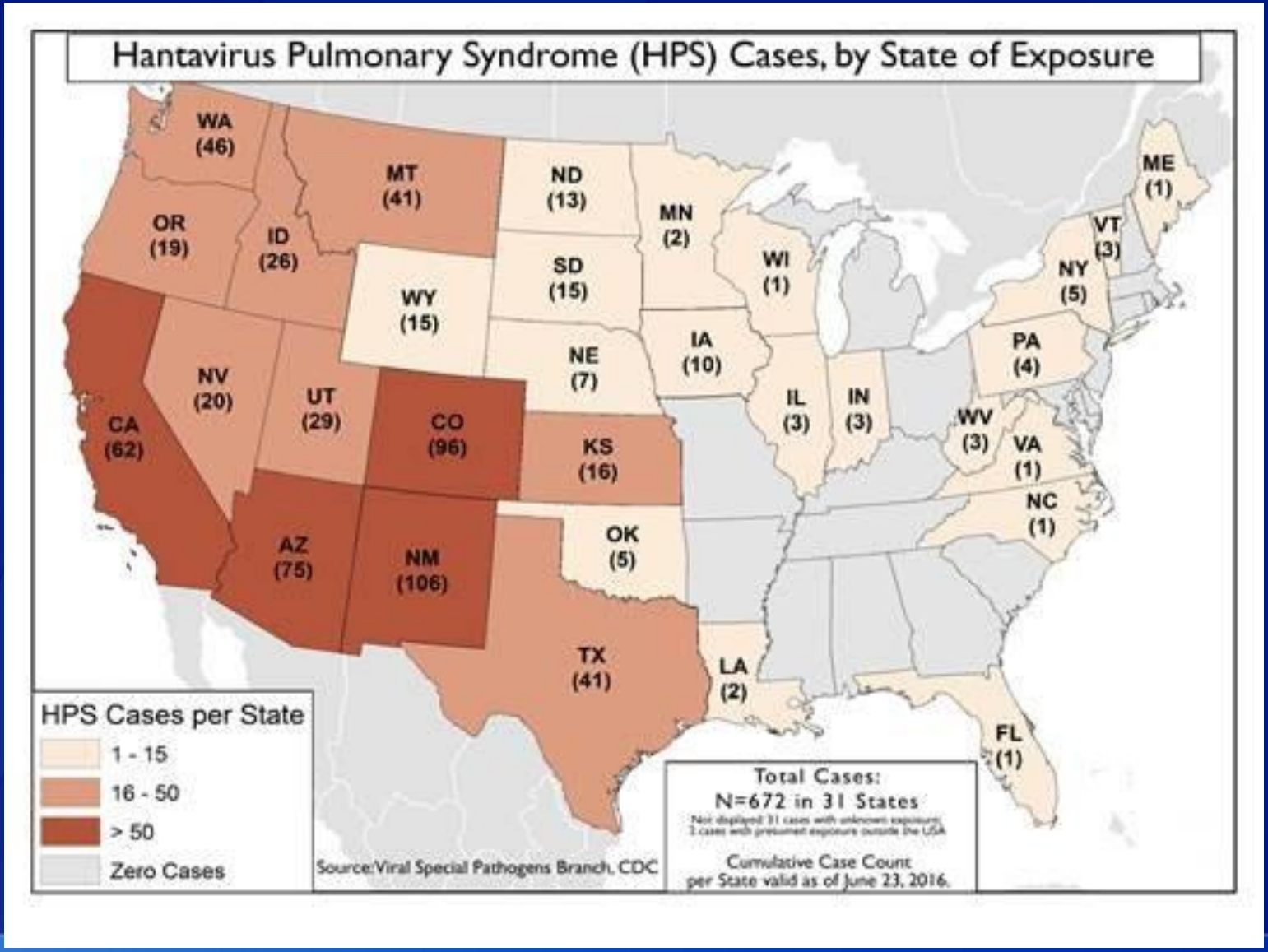
- Persons living or working in rural areas at increased risk
  - Farmers
  - Outdoor enthusiasts (camping, hiking)
  - Opening/cleaning unfrequented buildings and spaces (summer homes, sheds, attics, etc.)
- 20-40 cases reported annually, >95% exposed west of Mississippi River
  - Importance of exposure & travel history

Hantavirus Pulmonary Syndrome U.S. Descriptive Demographics

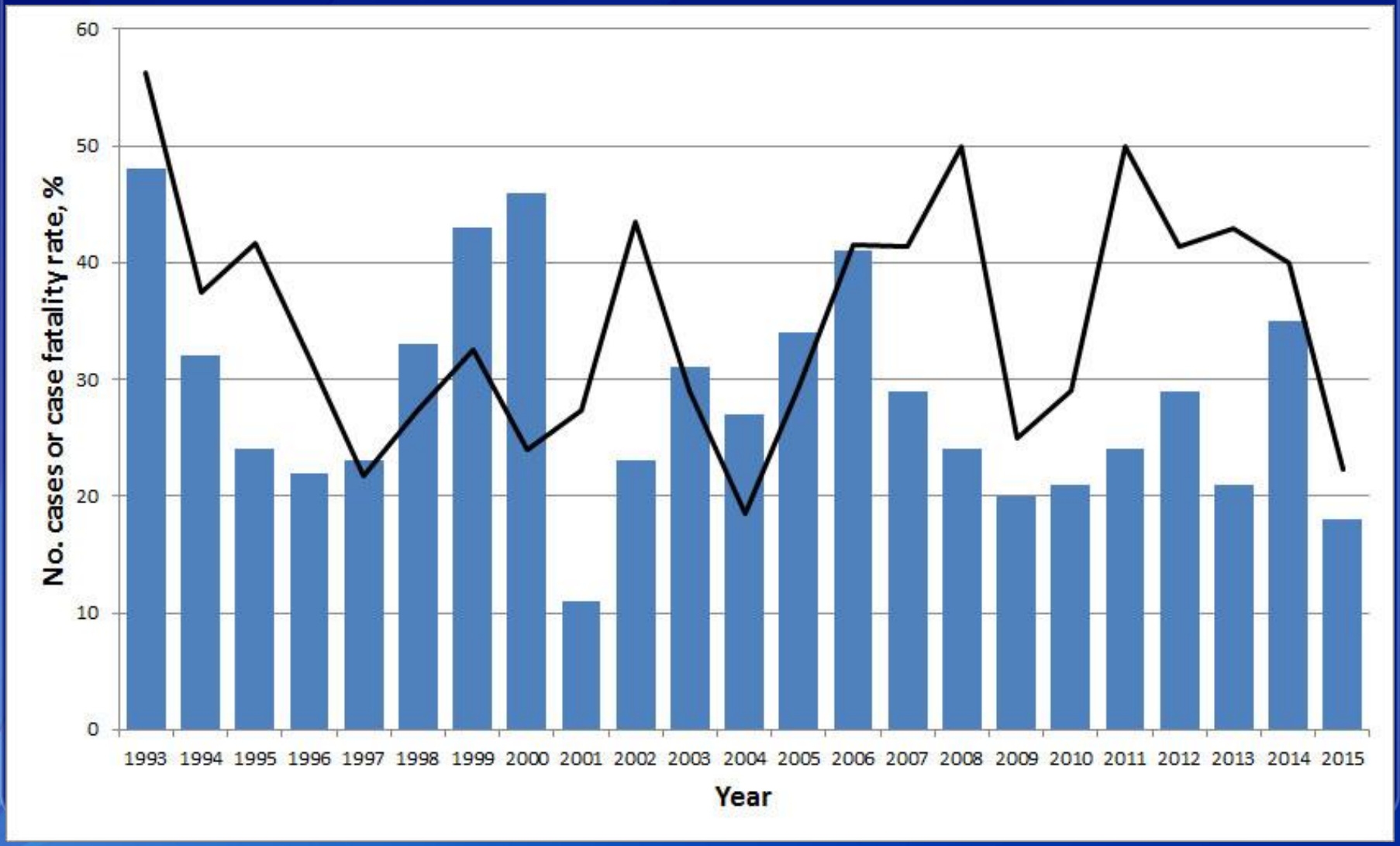
Characteristic		Total
Gender	Male	401 (63%)
	Female	236 (37%)
Race	White/Caucasian	496 (78%)
	American Indian	115 (18%)
	African American	12 (2%)
Ethnicity	Hispanic	127 (20%)
Outcome	Fatal	229 (36%)

- Total of 637 cases between 1993 and 2015
- Mean age: 37 (range: 5 to 84)

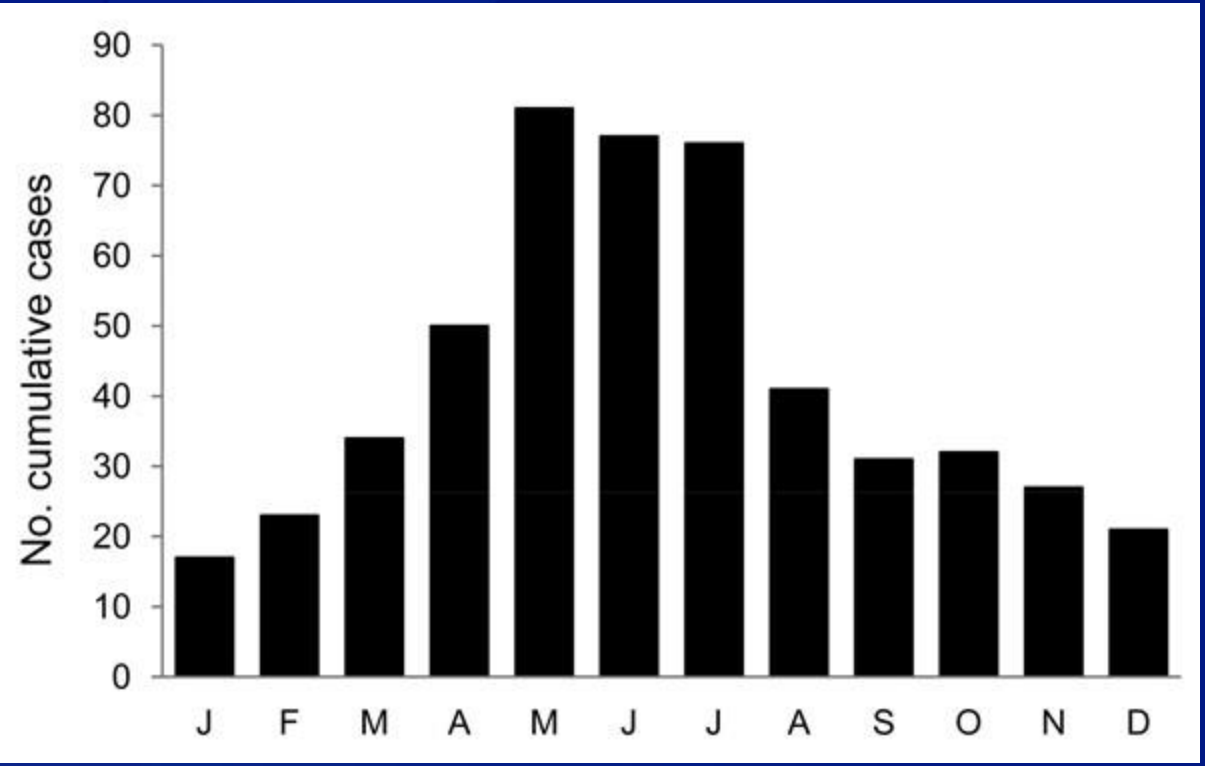
Hantavirus Pulmonary Syndrome Cases In the U.S. 1993-2015



Annual HPS Cases and Fatality Rate in the U.S. 1993-2015



Cumulative HPS Cases by Month of Onset in the U.S.



MacNeil A, Ksiazek TG, Rollin PE. Hantavirus pulmonary syndrome, United States, 1993–2009. Emerg Infect Dis [serial on the Internet]. 2011 Jul [*date cited*]. http://dx.doi.org/10.3201/eid1707.101306

Hantavirus Diagnostics

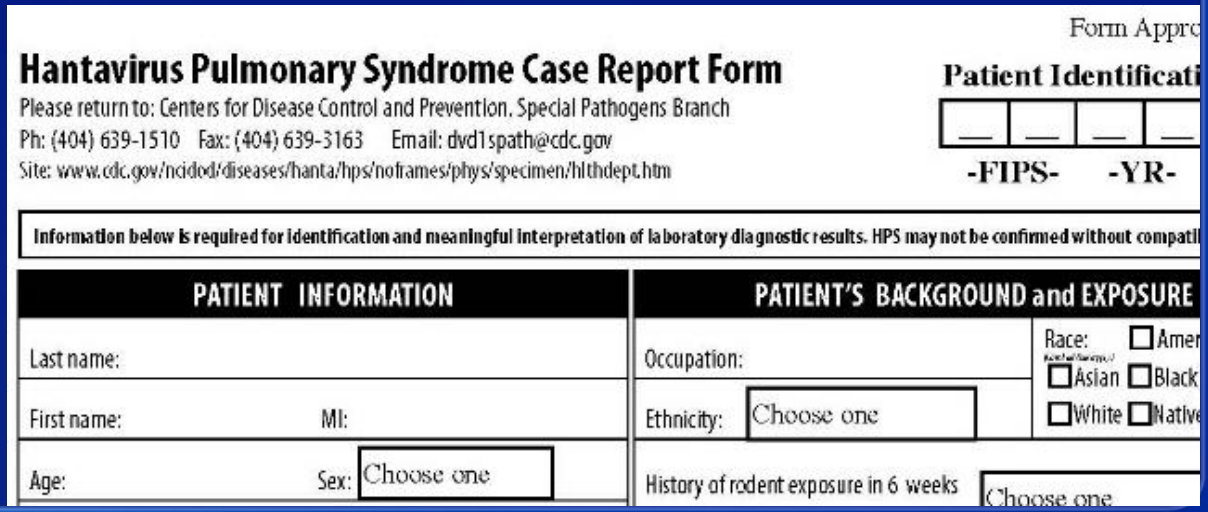
- **Serology:** Most common means of diagnosis in US; detects IgM & IgG
  - Testing available through commercial and public health labs (state/federal)
- **PCR:** Detectable virus during acute phase
- **Immunohistochemistry:** postmortem detection of hantavirus antigen

Hantavirus Antibody Testing

- IgM & IgG develop rapidly after onset of symptoms– detectable at first test in nearly all HPS patients
- Cross-reactivity between different hantavirus species
- Commercial assay:
  - False positive results possible; important to interpret results carefully
- CDC ELISA:
  - Available through state & federal labs; highly sensitive & specific

HPS Surveillance

- HPS and hantavirus infection without pulmonary symptoms are nationally notifiable conditions
  - Providers should contact local or state health department for awareness & assistance with diagnostic testing
  - Environmental investigations may occur at exposure sites
  - Access form at http://www.cdc.gov/hantavirus/pdf/hps_case-report-form.pdf



Form Appro

Hantavirus Pulmonary Syndrome Case Report Form

Please return to: Centers for Disease Control and Prevention, Special Pathogens Branch
Ph: (404) 639-1510 Fax: (404) 639-3163 Email: dvd1spath@cdc.gov
Site: www.cdc.gov/ncidod/diseases/hanta/hps/noframes/phys/specimen/hlthdept.htm

Patient Identificati

-FIPS- -YR-

Information below is required for identification and meaningful interpretation of laboratory diagnostic results. HPS may not be confirmed without compati

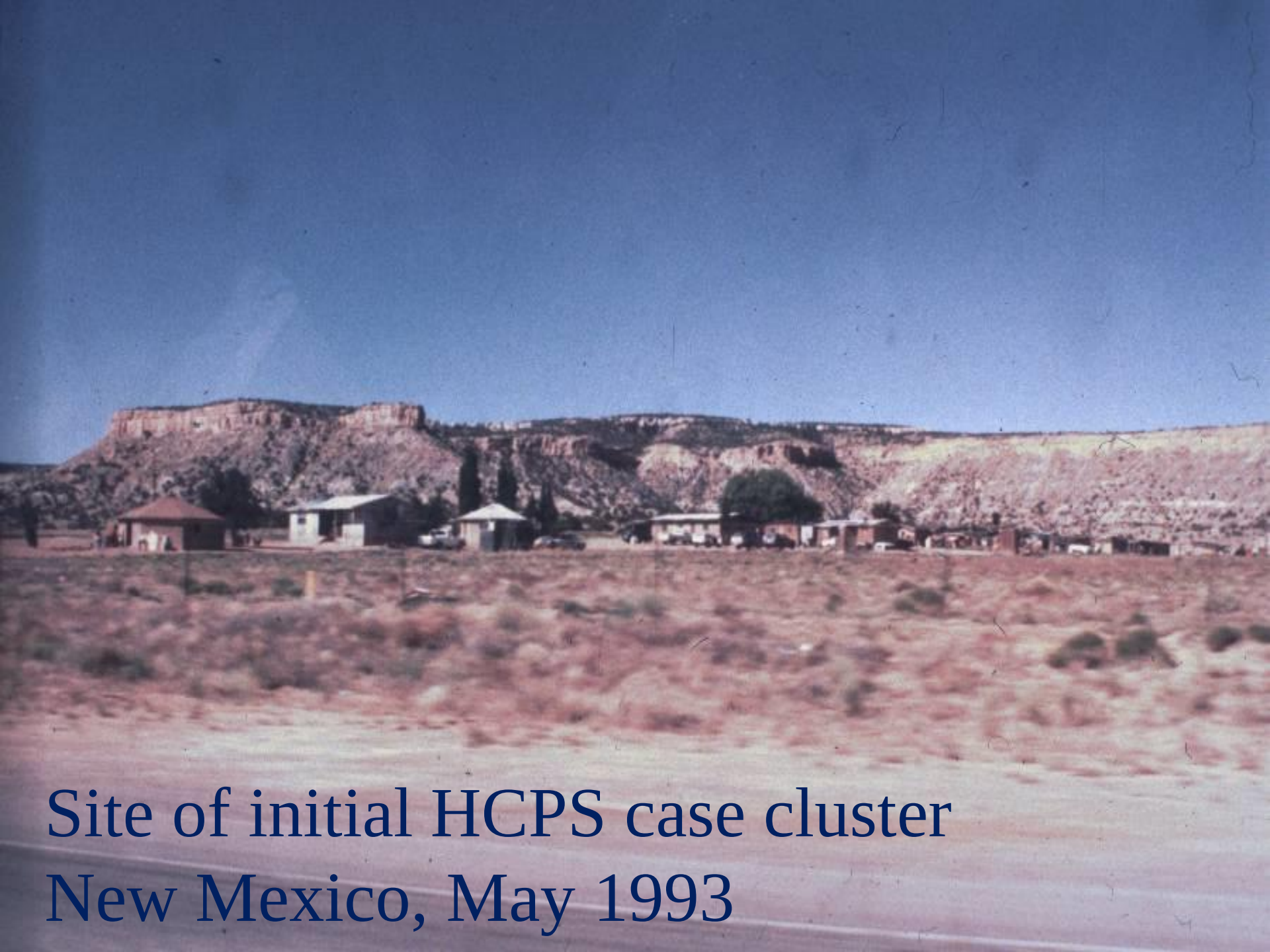
PATIENT INFORMATION		PATIENT'S BACKGROUND and EXPOSURE	
Last name:		Occupation:	Race: Amer / Asian Black / White Native
First name:	MI:	Ethnicity: Choose one	
Age:	Sex: Choose one	History of rodent exposure in 6 weeks	Choose one

HCPS: Incubation Period, Clinical Presentation and Course

Gregory Mertz, M.D.

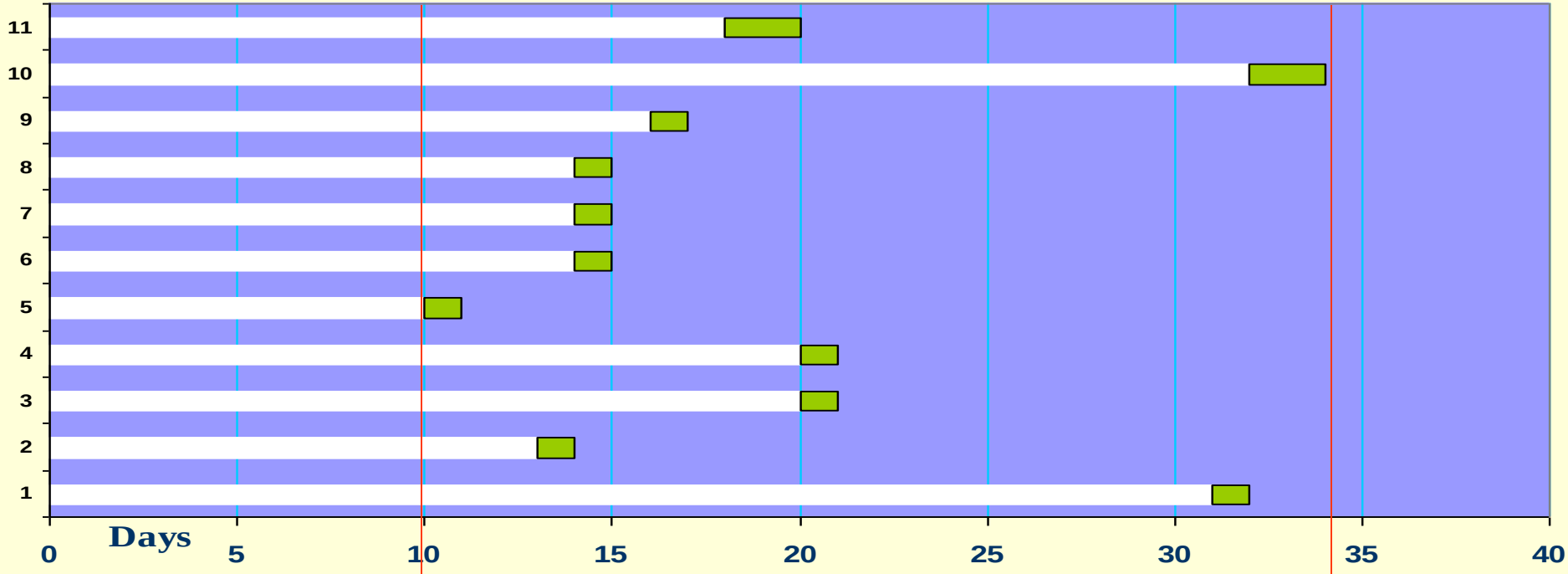
Professor of Internal Medicine
University of New Mexico

June 30, 2016



Site of initial HCPS case cluster
New Mexico, May 1993

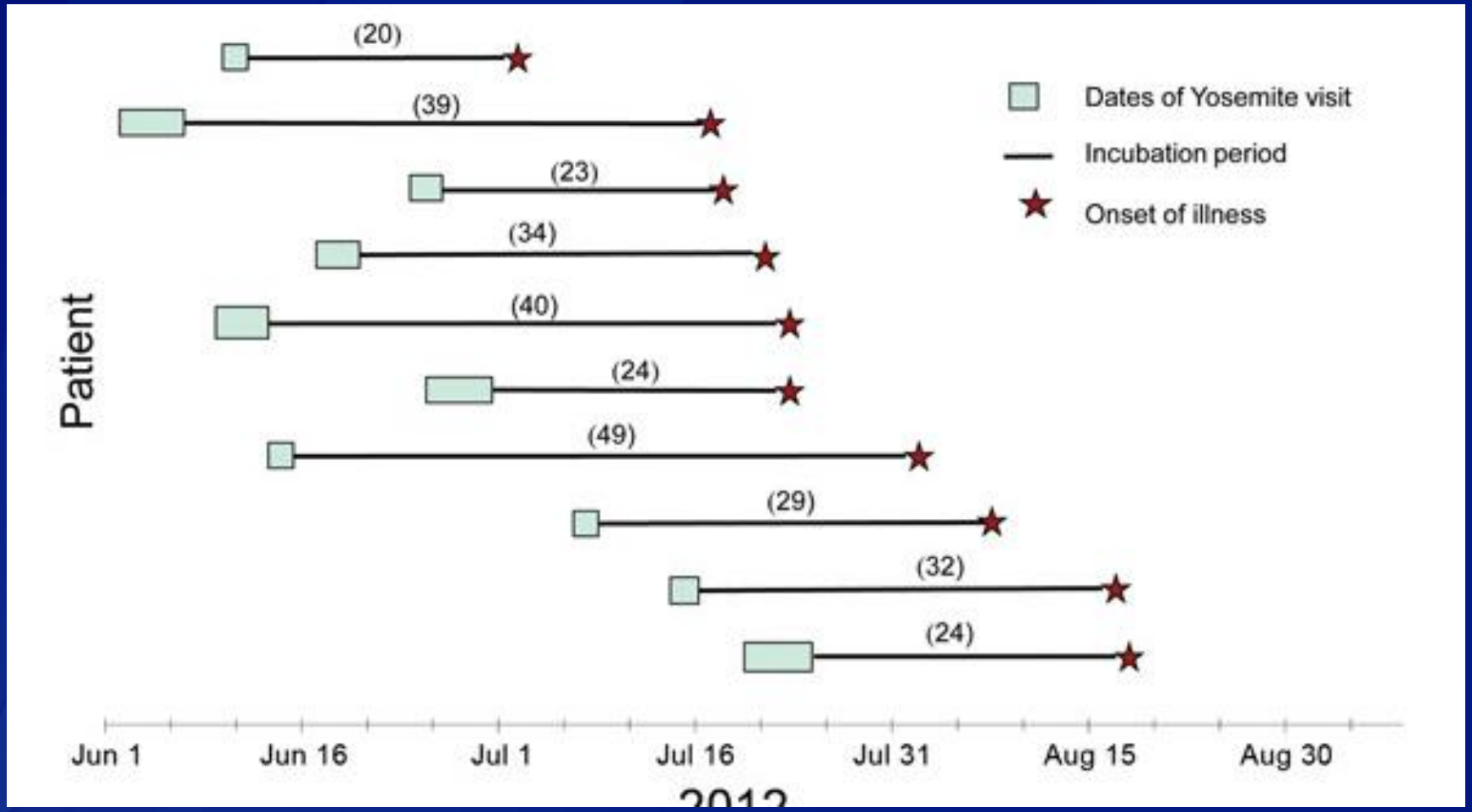
Incubation period, Andes virus (ANDV) Infection, Chile
11 patients with 24-48 hrs of exposure in rural area



Mean: 18.3 days
Range: 10-34

Vial P, et al. Emerg Infect Dis 2006:12:1271-3. PMID: 16965713

2012 Yosemite Sin Nombre Virus outbreak
Incubation: median 30.5 (range 20-49) days



Nunez JJ, *et al.* Emerg Infect Dis 2014;20:386.

Detection of Andes virus (ANDV) RNA by reverse-transcription polymerase chain reaction (RT-PCR) in peripheral blood cells obtained from household contacts who were asymptomatic and seronegative at study entry

Additional household case patient no. from table 3 (sex, age in years)	Viral level in first positive sample, ANDV copies/mL of sedimented peripheral blood cells	Days from first positive RT-PCR to		Days from onset of symptoms in index case patient to positive RT-PCR in contact
		Onset of prodromal symptoms	Onset of cardiopulmonary phase	
16 (M, 47)	28,244	14	18	18
15 (M, 34)	33,000	15	18	15
13 (F, 48)	18,342	7	10	18
10 (F, 2)	1,181,551	NA[a]	12	~14[b]
14 (M, 50)	116,754	5	8	22
9 (F, 47)	3882	NA[c]	7	19

NOTE. NA, not available.

[a] Case patient 10 was afebrile, asymptomatic, and seronegative when ANDV RNA was detected by RT-PCR, but the day of onset of prodromal symptoms could not be determined because of the subject's age.

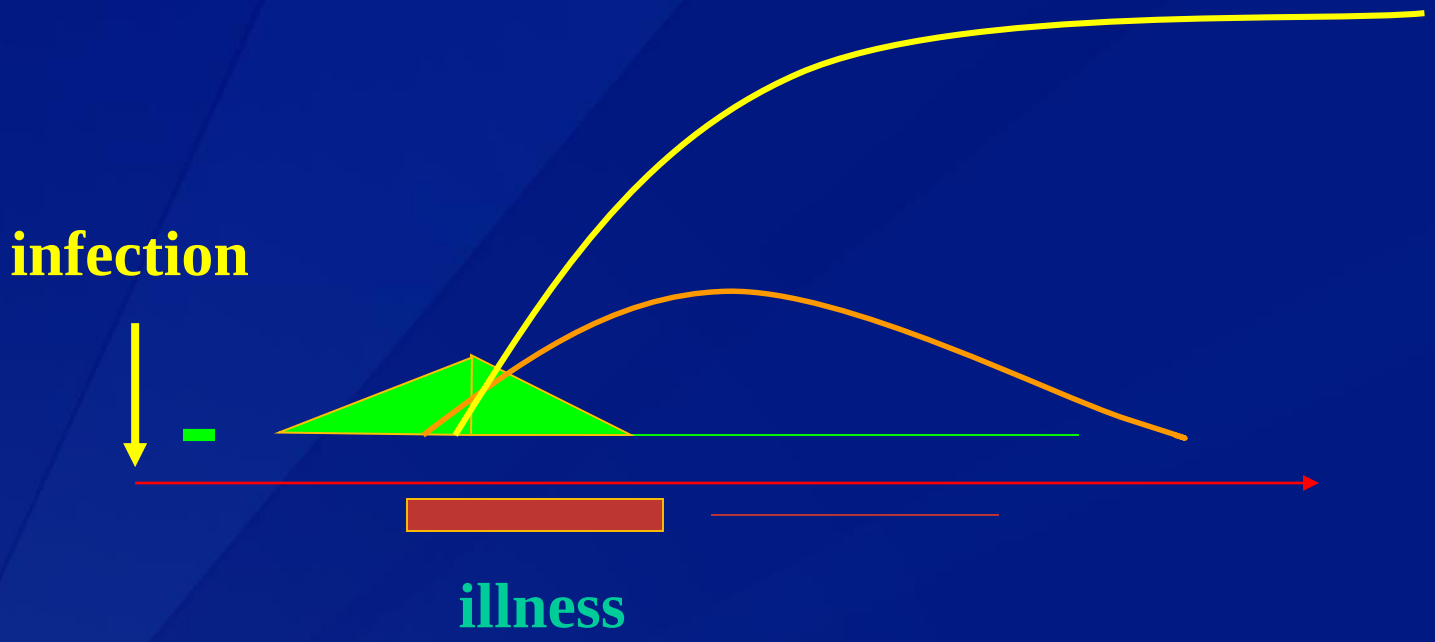
[b] First positive PCR result on 1 June; the index case patient died on 21 May after several days of symptoms, but the exact date of the onset of symptoms was not known.

[c] Case patient 9 was seronegative when enrolled 7 days before the day of the onset of symptoms, but cells were not collected for analysis by RT-PCR at the enrollment visit.

Ferrés M, et al. J Infect Dis. 2007;195:1563-1571. PMID: 17471425

The Journal of Infectious Diseases

Infection with Hantavirus



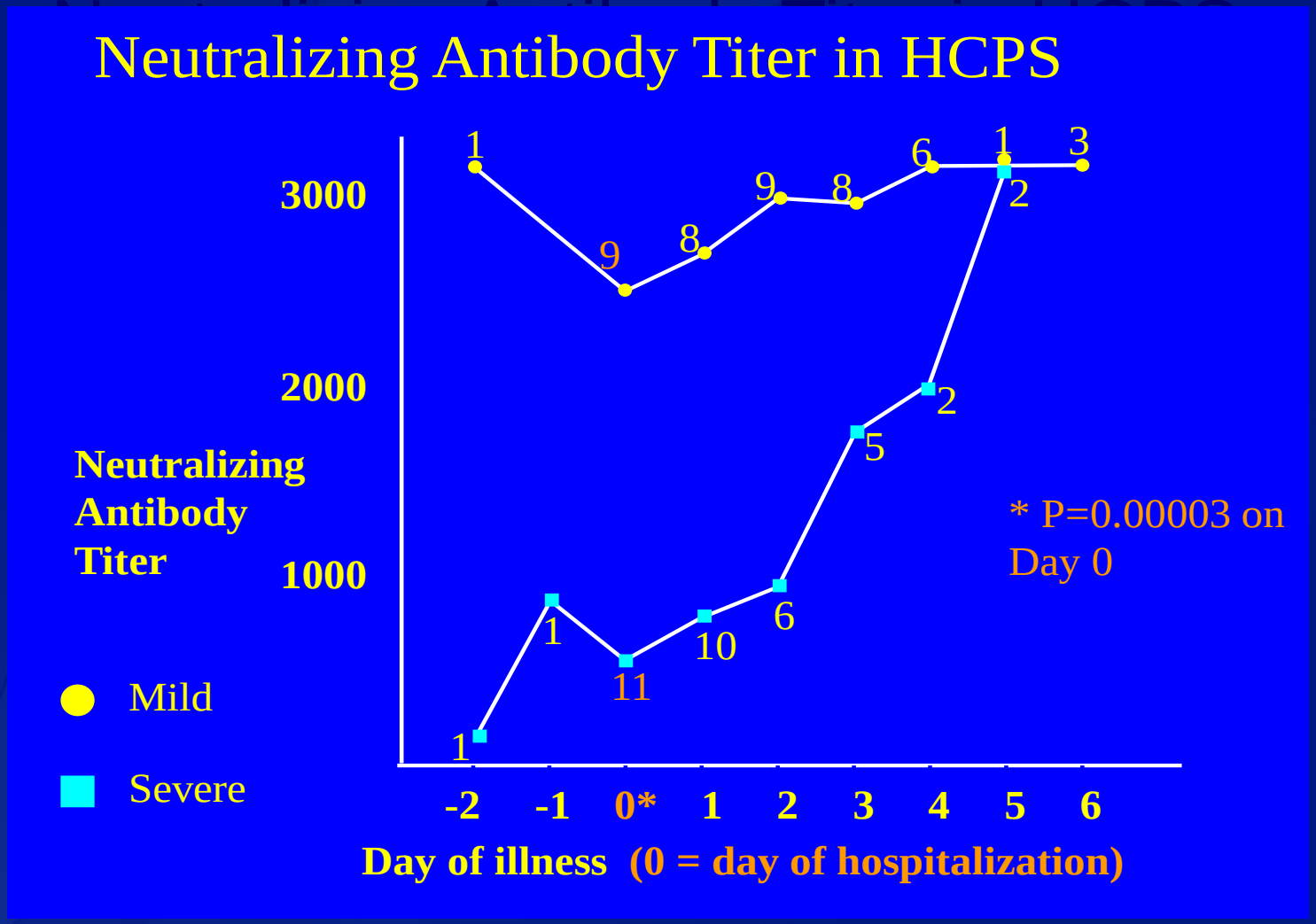
viremia

virus in cells

IgG

IgM

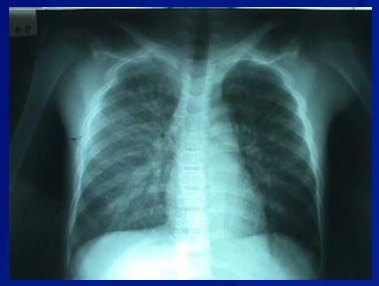
Neutralizing Antibody Titer in HCPS

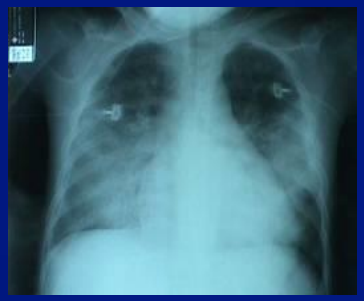
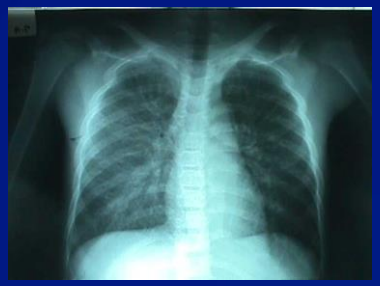


At hospital admission, patients who have a mild course of HCPS have significantly higher anti-Sin Nombre virus (SNV) neutralizing antibody titers when compared to patients who have or progress to severe or fatal disease.

(Bharadwaj M, *et al*, J Infect Dis, **2000**; 182(1):43-8. PMID: 10882580).

HCPS Presentation



Fever

Respiratory failure

Shock

↑ Hematocrit

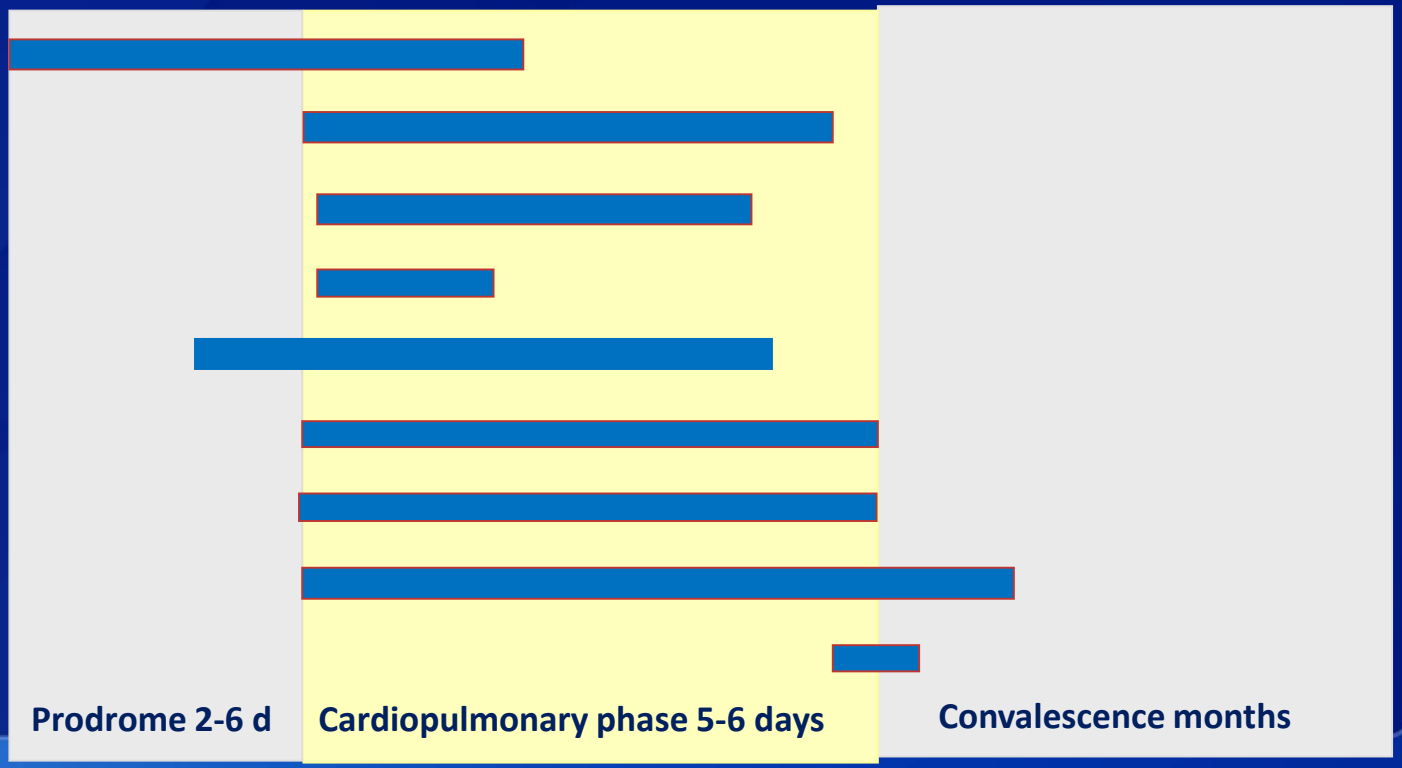
↓ Platelets

↑ Immunoblasts

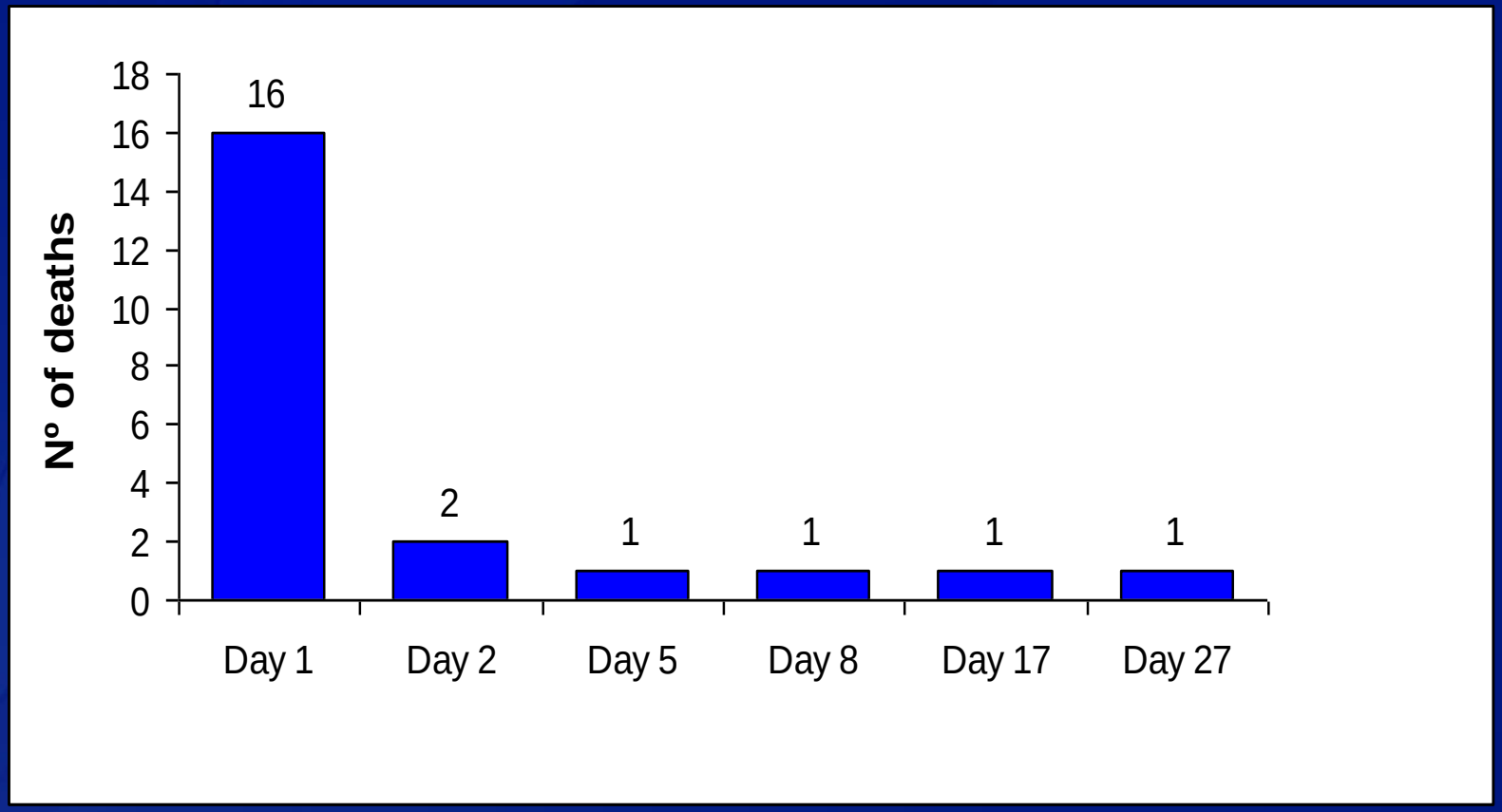
Leukocytosis

↑ Liver enzymes

Diuresis



Deaths by hospital day among 104 hospitalized HCPS cases in Chile



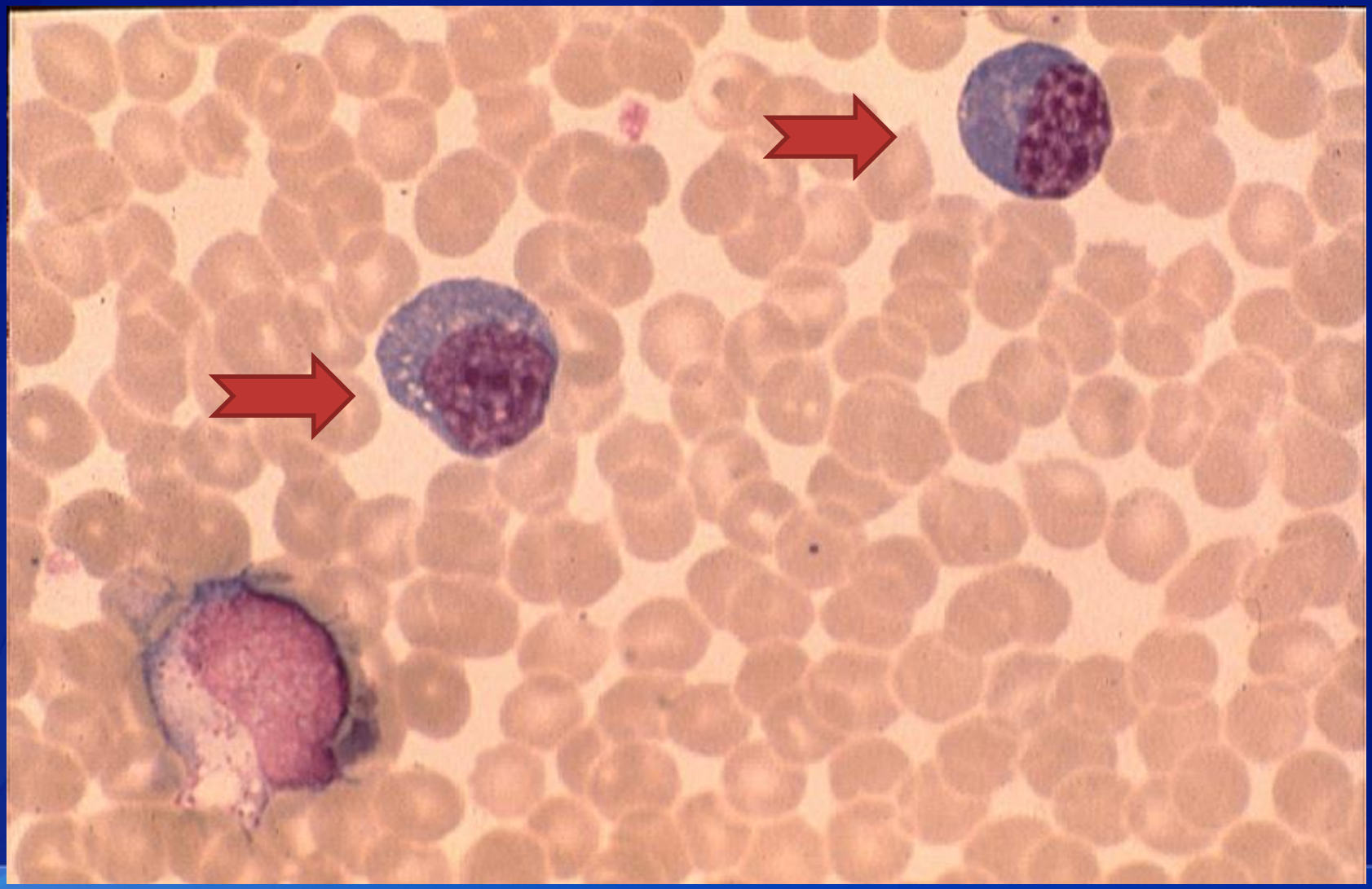
Presumptive diagnosis in cardiopulmonary phase

***After the onset of pulmonary edema*, the presence of 4 of 5 findings has a sensitivity of 96% and specificity of 99%**

- Thrombocytopenia
- Myelocytosis
- Lack of significant toxic granulation in neutrophils
- Hemoconcentration
- More than 10% lymphocytes with immunoblastic morphologic features

Koster F, et al. Am J Clin Pathol 2001;116:665-72. PMID: 11710682

Immunoblasts in HCPS appear early in cardiopulmonary stage

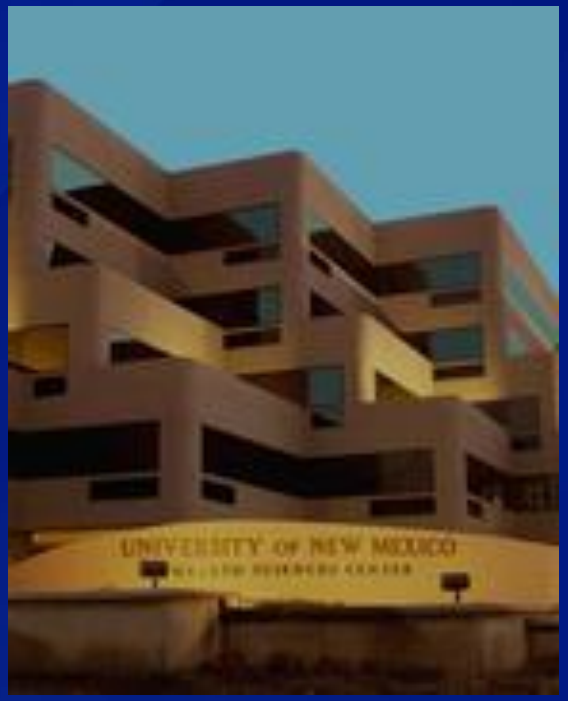


Presumptive diagnosis of HCPS in the CASG IV ribavirin trial

- In 24 subjects with suspected HCPS in the cardiopulmonary phase (with bilateral infiltrates and hypoxia), SNV infection was confirmed in 23 (96%) with a presumptive diagnosis based on smear evaluation
- In 12 subjects with suspected HCPS in the febrile prodrome (with fever and thrombocytopenia), none had SNV infection.

Mertz GJ, *et al*. Clin Infect Dis. 2004:1307-13.

Hantavirus:
A Tale of Mice and Men



Michelle Harkins, MD

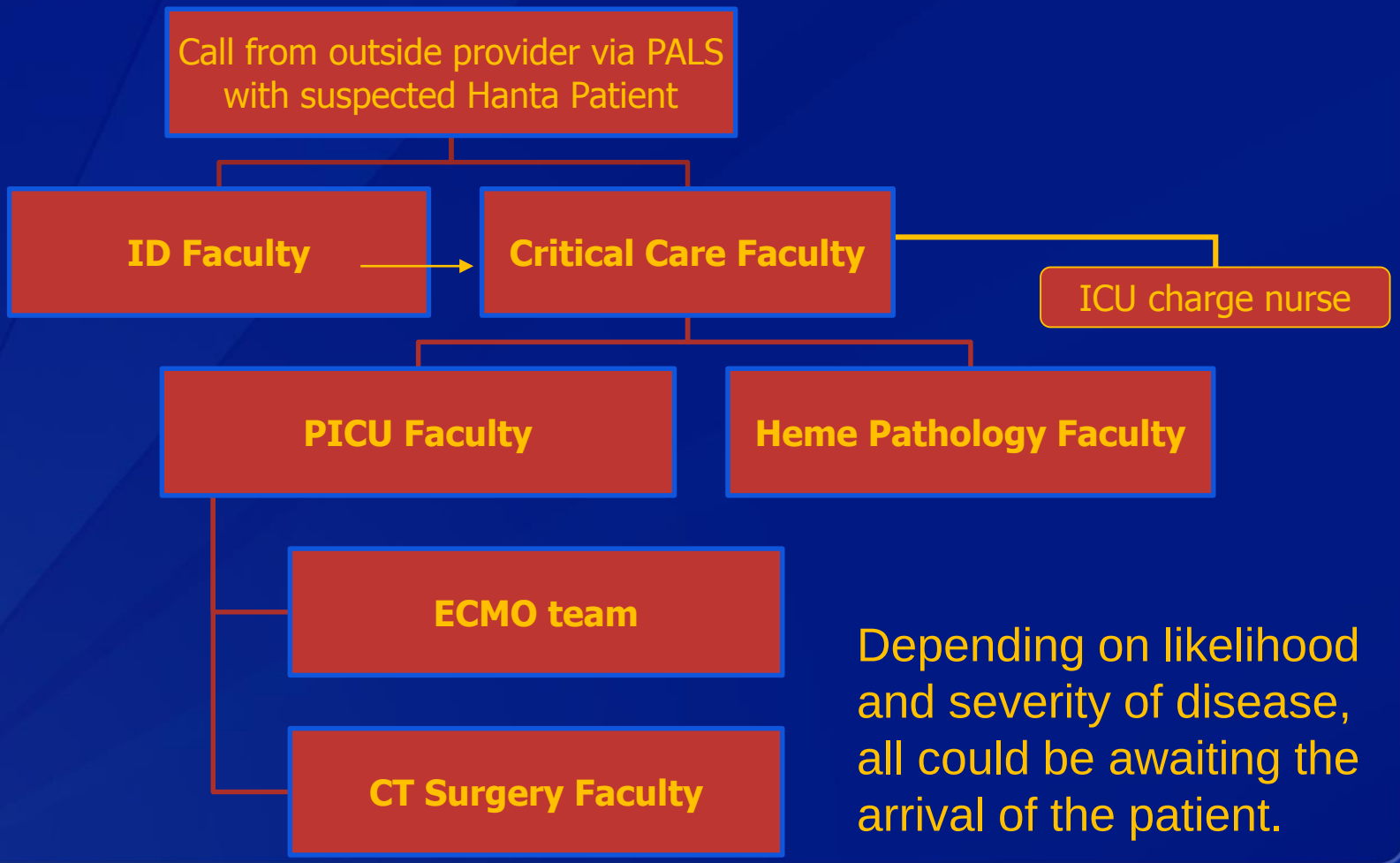
Diagnostic Dilemma

- Patients may present with vague symptoms
- Return for CBC in 8-12 hours
- If platelet count is falling, call **1-800-272-2000** (at UNM Med Center), ask for Medical Critical Care or ID physician on call to discuss

Triage and Treatment

- **Key point:** transfer patient prior to cardiopulmonary phase to tertiary care center, preferably one with ECMO
- Don’t wait to stabilize
- AVOID fluid resuscitation
- Inotropes early
- Oxygen, try to avoid intubation
- Arrange air transport with ability for pressor initiation and to a center with ECMO capability

Multidisciplinary Involvement in Treatment of HCPS



Depending on likelihood and severity of disease, all could be awaiting the arrival of the patient.

Ribavirin

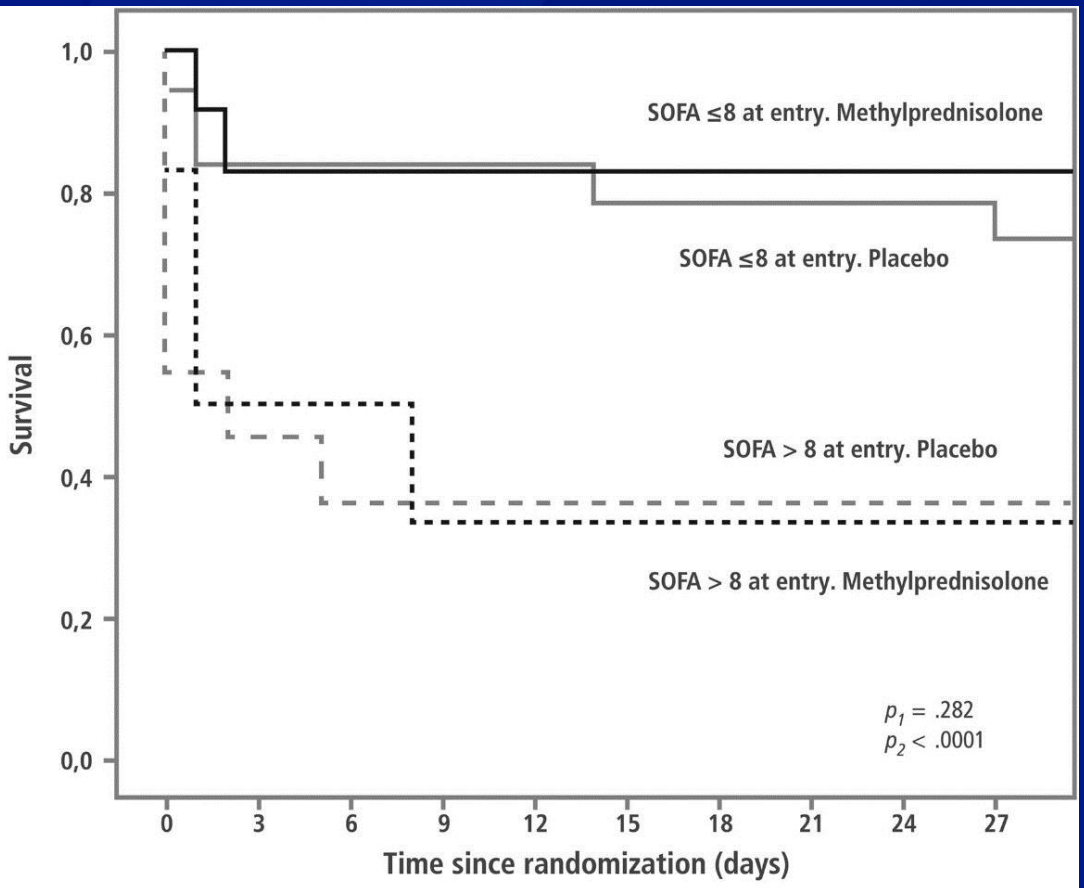
- Given early in HFRS in China, 7-fold reduction in mortality risk
- Results in HCPS inconclusive
  - Does inhibit SNV *in vitro*
  - Pre-treatment reduced deer mice sero-conversion
- *in vitro* and *in vivo* inhibition ANDV
  - Provided protection in a lethal hamster model of HCPS
  - ? Beneficial for post-exposure prophylaxis

Jonsson, Clin Micro Rev, April 2010; Safronetz, Plos One, Aug 2011

Survival without ECMO
Ribavirin versus Placebo Recipients

Mertz GJ, et al. Clin Infect Dis, 2004 (Nov 1);39:1307-1313.

Kaplan-Meier survival analysis by treatment arm (methylprednisolone vs placebo) and severity at entry by sequential organ failure score (SOFA)



Number at risk

Methyl prednisolone	30	27	23	22	22	15	22	22	22	22
Placebo	30	21	20	20	20	20	19	19	19	18

Vial P A et al. Clin Infect Dis. 2013;57:943-951

Immune serum

- Serum from survivors with neutralizing antibodies may combat the viremia present
- Hamster/rat/primate studies have shown passive protection from hantavirus challenge when given neutralizing Ab
- No controlled human trials
- Not available in the US

Safronetz, Plos One, Aug 2011

Management of HCPS

- Critical care management
- Monitor PaO_2/FiO_2, cardiac index, lactate
- Pressors rather than IV fluids
- If ECMO is available,
  - Early placement of vascular sheaths
  - Concurrent intubation and initiation of ECMO if medical management fails
- No role for ribavirin or methylprednisolone (ineffective in placebo-controlled trials)

Why ECMO for HCPS?

- Early experience showed short duration of critical condition
- Autopsy findings without tissue damage- circulating inflammatory mediators likely cause cardiopulmonary dysfunction
- Occurs in previously healthy patients

Criteria for ECMO

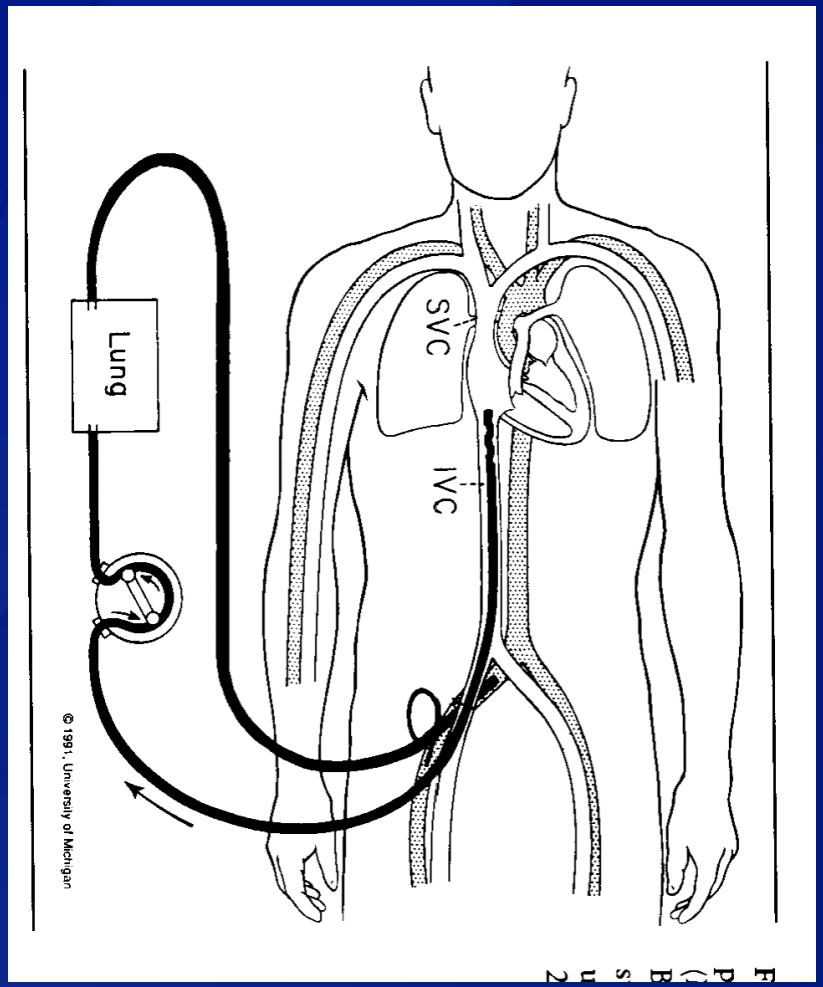
- ≤ 65 years of age
- No major organ system failure (cirrhosis, ESRD, neurologic dysfunction)
- HCPS by history, clinical judgment, smear
- CI<2.5 despite resuscitation or rapidly declining clinical status
- Hypotension
- Hypoxemia – PaO_2/FiO_2 <50 despite support

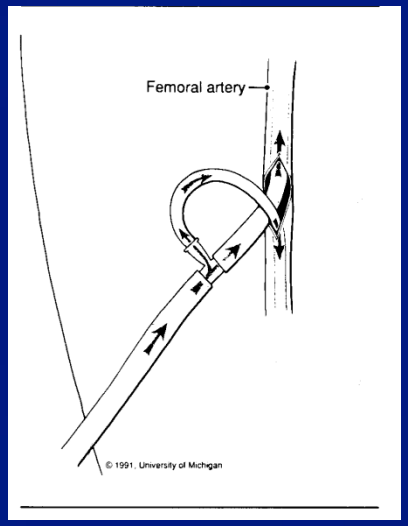
UNM Memo; Crowley, Crit Care Med, 1998

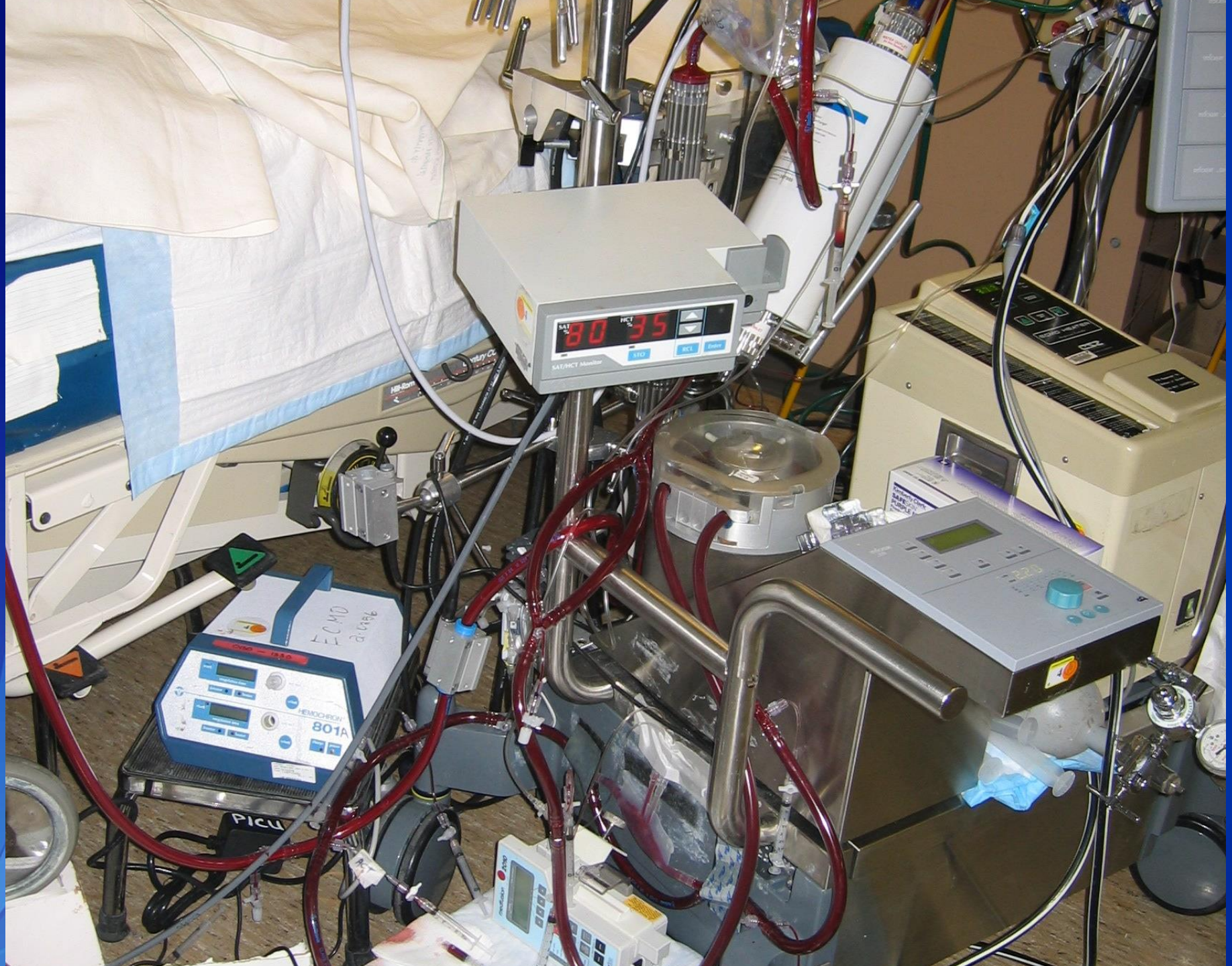
HCPS-ECMO Cannulation

- Femoral site-venoarterial
  venous- 27- 29 french
  arterial- 16-18 french
- Distal perfusion cannula – via posterior tibial artery
- Open vs. percutaneous- surgeon's preference
- Right IJ 27 to 29 french for additional drainage

Extracorporeal Membrane Oxygenation (ECMO)






80
35
SAT/HCT Monitor
801A
PICU

Typical ECMO Course

- Patient paralyzed and sedated
- Ventilator settings ~ SIMV 10/500cc/40%/10
- Hemodynamic improvement 12 hours
- Pulmonary improvement 48-72 hours
- Weaning from ECMO 4-5 days when pulmonary capillary leak resolves and cardiac function improves

Crowley, Crit Care Med, 1998

UNM Hanta Stats

- From 2000 to 5/16
  - Approximately 75 patients Hanta +, not all needed ECMO
- Several patients with HCPS died prior to or during transport to UNM
  - 2 within the last few months
    - From Four Corners area
      - One presented with GI complaints first day then represented next day in shock
      - Other one presented late

UNM ECMO Hanta Stats

- Total 59 patients: 04/15/1994 – 3/29/16
  - Survived ECMO 43/59 (73%)
  - Survived to hospital discharge 37/59(63%)
- Age range 9 - 69
- Male 32, Female 27
- Duration of ECMO 5-276 hours (143)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To Ask a Question

- **Using the Webinar System**
  - “Click” the Q&A tab at the top left of the webinar tool bar
  - “Click” in the white space
  - “Type” your question
  - “Click” ask

- **On the Phone**
  - Press Star (*) 1 to enter the queue
  - State your name
  - Listen for the operator to call your name
  - State your organization and then ask your question

Thank you for joining!
Please email us questions at coca@cdc.gov

Centers for Disease Control and Prevention
Atlanta, Georgia
http://emergency.cdc.gov/coca

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Upcoming COCA Call:

CDC Guideline for Prescribing Opioids for Chronic Pain (second call in a series of 4)

- Date: Wednesday, July 27, 2016
- Time: 2:00 – 3:00 pm (Eastern Time)

Free Continuing Education. Registration Not Required.

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