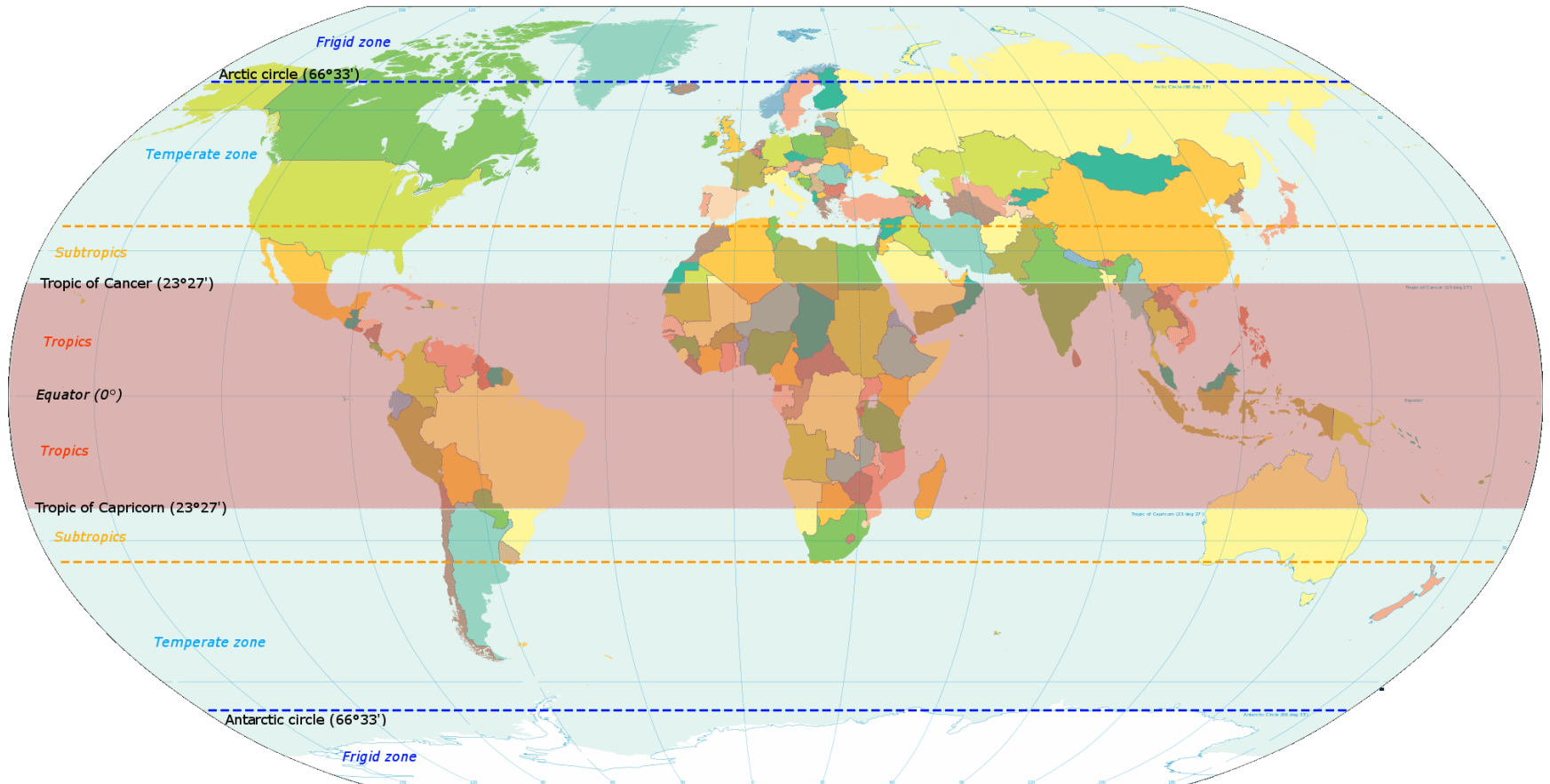


# Fever in the Traveler *in the tropics* – a case-based discussion

Holly Murphy, MD, MPH&TM  
CIWEC Travel Medicine Center  
Kathmandu, Nepal

# Perspective on “tropics”



*“Tropicality encompasses two contradictory imaginaries. The first is that the tropics are a sort of Garden of Eden, a heaven on Earth.<sup>[7]</sup> The second is that the tropics are primitive and essentially lawless.<sup>[7]</sup>”* Arnold, David. "Illusory Riches: Representations of the Tropical World, 1840-1950", p. 7. Journal of Tropical Geography

# Perspective on “fever”

- Fever with nonspecific symptoms
  - Fever curve
- Fever with rash
  - macular vs petechial
- Fever/headache/rash
- Fever/meningismus
- “outliers”



# characterize the exposures..

- Geographic location (itinerary)
  - Time from exposure/location
- Exposures
- Vectors
- Season
- Animals
- Sick contacts



# ...characterize the patient

- Underlying medical illness
- Age
- Chemoprophylaxis
- Economics of travel (ex. Backpacking guesthouses vs 5-star hotels)
- Cultural habits
- Vaccine history (ex. hep A, typhoid, influenza)



# Differential Diagnosis

- Dangerous
- Contagious
- Treatable
- Common
- Diagnostics available
- “typical” or “atypical”



# Case 1. Fever and rash

- 40 yo Belgium woman on retreat in Boudha, Kathmandu in Nepal for 2 months with fever x 7 days in February 2015
- Headache and cough, non-pruritic rash
- H/o PCN allergy – not anaphylaxis
- Vaccines Typhoid IM within 3 years; MMR, JE, Hep A and B, Influenza

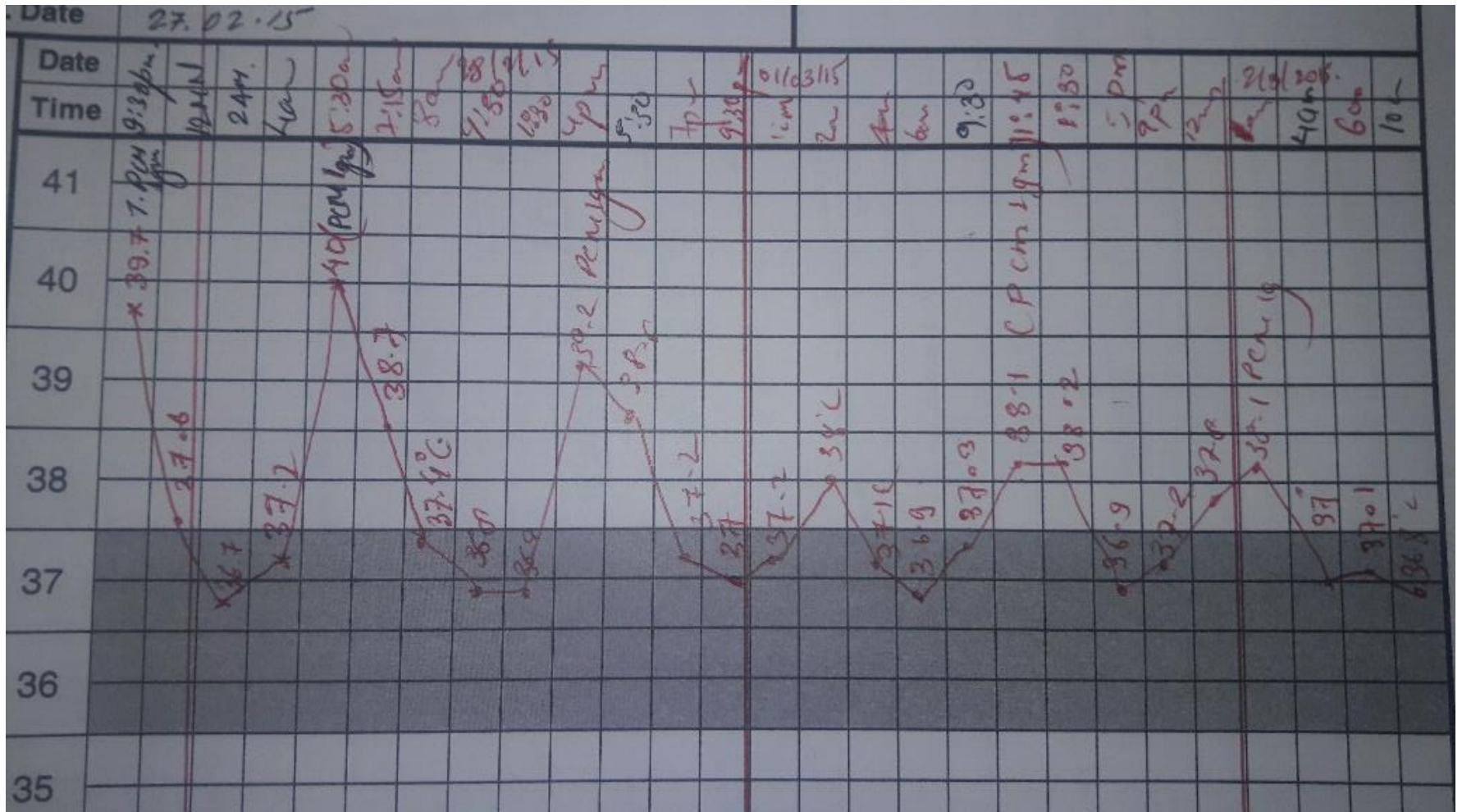


# Exam and Diagnostics

- T 39.7; P 104/min; BP 120/70
- Lungs CTAB
- Non-blanching maculopapular rash trunk/abdomen to forearms/thighs
- WBC 5200 (75N; 22L) Plt 150K
- ALT 101; AST 72; creat 0.7; Na 39
- CRP pos 96mg/L
- CXR LLL basilar consolidation



# Fever curve Day 1-3



Treatment: Azithromycin (Day 1); Ceftriaxone (added Day 2)

# Diagnostics

- Blood culture – routine and BHI
- Dengue IgM and NS1Ag (PanBio Diag, Korea)
- Malaria smear and Ag (CTK Biotec, US)
- Influenza NP swab (Quickvue, US)
- Leptospira IgM
- Measles IgM
- Rickettsial panel

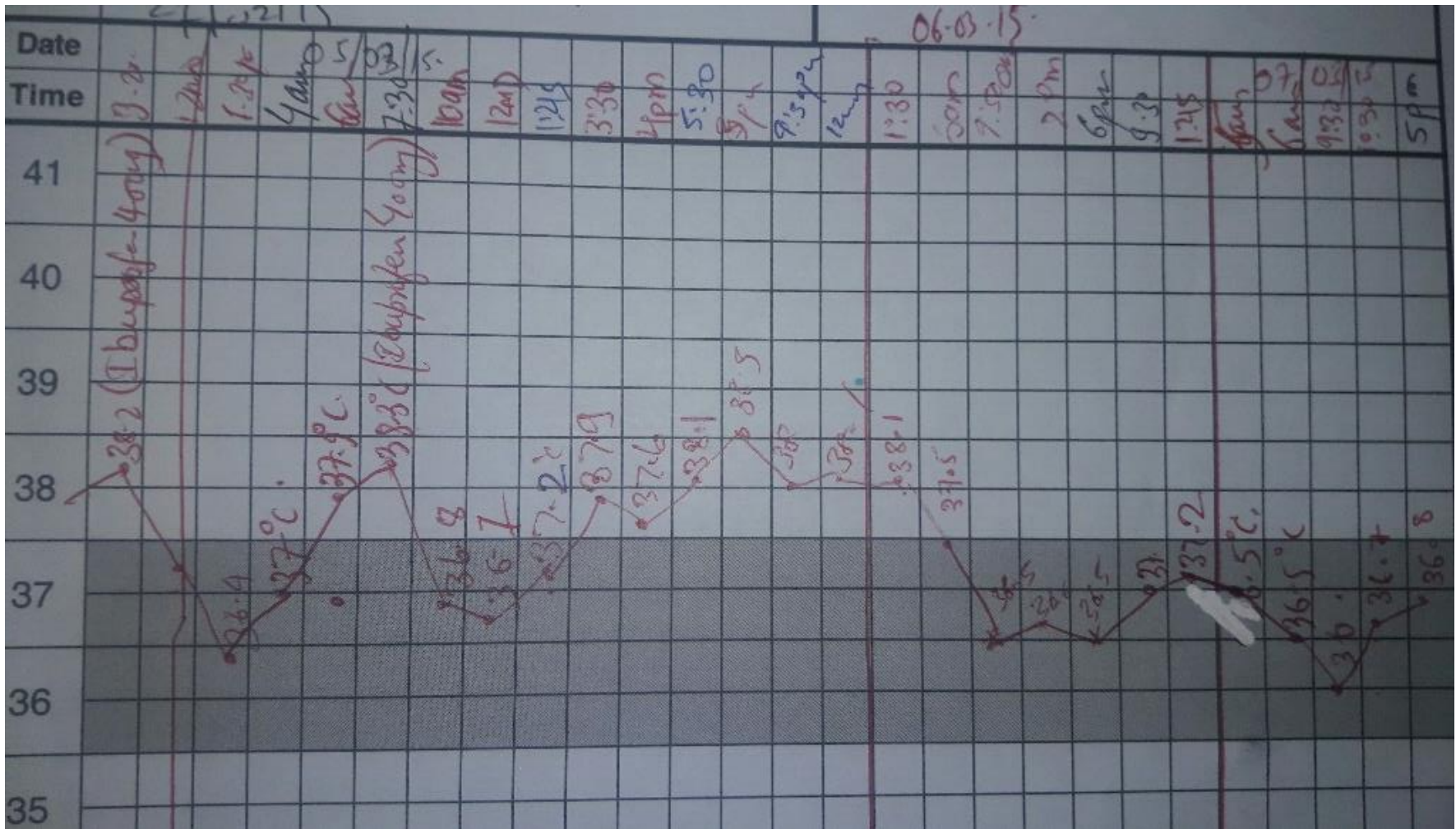
# Fever Curve Day 3-5



# Clinical Course

- Day 4 T spike to 39.7 with chills; rash improving
- AST/ALT 280/375
- Doxycycline added

# Fever Curve Day 6-7



# Diagnostics

- Measles IgM equivocal at 8.35 (Neg <8; Post>12 Ref Lab India)
- Murine typhus (IgM) positive
- Patient noted a woodpile outside of room at Monastery with scurrying rats!

# Murine typhus

- *Rickettsia typhi*
- Rat/rodent reservoir
- Vector: Asiatic rat flea *Xenopsylla cheopsis*
- Inoculation of flea feces in bite wound
- Murine-typhus “look-alike” – *Rickettsia felis* (cat fleas)
- Complications: aseptic meningitis, deafness, deep venous thrombosis, and even death
- Traveler reports:
  - Asia (Nepal, India, Thailand, Indonesia, China, and Vietnam),
  - Africa (Morocco, Gabon, Botswana, and Guinea Bissau), and
  - Europe (Cyprus, Greece, and Spain)

# Causes of fever in a Nepali hospital

876 patients enrolled, pathogens identified in 323 (37%). No dengue or malaria seen.

Salmonella Typhi-----	60
Salmonella Paratyphi-----	57
R. Typhi (murine typhus)-----	97
Strep Pneumoniae-----	53
Leptospirosis-----	36
Orientia Tsutsugamushi (scrub typhus) -----	28



# Case 2. Fever and Rash

- 67 year-old expatriate New Zealander woman admitted to CIWEC in April with 5 days fever
- Associated headache, arthralgias, diarrhea
- Lived outskirts of Kathmandu for 30 yrs
- 3 months prior had 1-mo visit to Queenstown, NZ with 2-day stop-over Bangkok
- Worked with wild dog protection
- Pet dog: daily walks in Shivapuri Forest
- Unsure of vaccination history

# Exam and Diagnostics

- T 40.3C, unremarkable exam
- WBC 6500 cells/mm<sup>3</sup> – polymorphonuclear predominance; Plt 63,000
- Ceftriaxone 2 g on admit

# Clinical Course

- Worsening within first 48 hr
- Persistent fever – Tmax 38.4C
- Photosensitivity, tinnitus, frontal HA, insomnia, confusion
- Cough, hypotension, tachycardia, hypoxia (pOx 88% with 2L O2)
- Exam: Developed edema peripheral and pulmonary (day 7 fever)
- disoriented; bil deafness; (nonblanching) purpuric rash with palmar/sole predilection



# Diagnostics

- Creatinine 2 mg/dL (0.8 baseline)
- AST 105; AP 765 U/L
- Plt 40, 000/mm<sup>3</sup>
- CXR: Bil interstitial infiltrates
- Blood cultures
- Leptospira IgM
- Mycoplasma IgM
- Serum held for rickettsial studies

# Rickettsia Testing, Marseilles

Species	Apr 20	Apr 24	Apr 29	May 15
R honei	Neg	256/32	512/32	1024/64
R felis	32/0	265/16	256/16	256/16
R massiliae	Neg	Neg	Neg	128/16
R aeschlimannii	Neg	Neg	NEG	128/16
R conorii	Neg	Neg	Neg	128/16
R slovaca	Neg	Neg	Neg	128/16
R hlijongangensis	Neg	32/32	64/32	128/16
R. AT1	Neg	32/32	64/32	64/32
R. Africae	Neg	32/32	64/32	64/32
R japonica	Neg	32/32	64/32	64/32
R typhi	Neg	Neg	Neg	64/64
R prowazekii	Neg	Neg	Neg	64/64
Orientia tsutsugamushi ser Kawasaki	Neg	Neg	Neg	64/64
O. Tsutsugamushi ser Gilliam	Neg	Neg	Neg	Neg

# Clinical Course

- Doxycycline 100 mg BID (PO) x 14 d
- Defervescence day 16
- Persistent tinnitus and residual high-tone deafness

Confirmed by RT-PCR: *R. honei*

# *R honei*

- New species 1998, Flinders Island Spotted Fever
- various tick species:
  - *Ixodes granulatus* (Thailand) and *Haemaphysalis novaeguineae* (Australia) –rats,
  - *Aponoma hydrosauri* ticks ( *Bothriocroton hydrosauri*) (Flinders Island, Australia) - reptiles
- ? ectoparasites associated with migrating birds that feed on local reptiles may transmit *R. honei* to reptile ticks.
- Human cases: Australia and Thailand
  - Spring and summer; no deaths reported
- Common features: headache, myalgia, cough, arthralgia, and maculopapular to purpuric rash; eschar is reported in 50% of cases
- Prior SFG rickettsioses have only been suspected in Nepal
- Isolation of strain TT-118 from a *Rhipicephalus haemaphysaloides* ticks in Nepal (*Jelinek T, Loscher T. Clinical features and epidemiology of tick typhus in travelers. J Travel Med 2001; 8:57–9.*)
- *Ix. granulatus* ticks found in Nepal



# Other Rickettsia in Travelers

- *R africae* (African Tick Bite Fever) – most common; cattle ticks; eschars/lymphadenitis/HA/vesicular rash; Africa-Caribbean
- *R conorii* (Mediterranean Spotted Fever)-dog ticks; eschar; Europe-Asia-Africa
- *Orientia tsutsugamushi* (Scrub typhus)- esp near rice fields, military; larval trombiculid mites (chiggers).

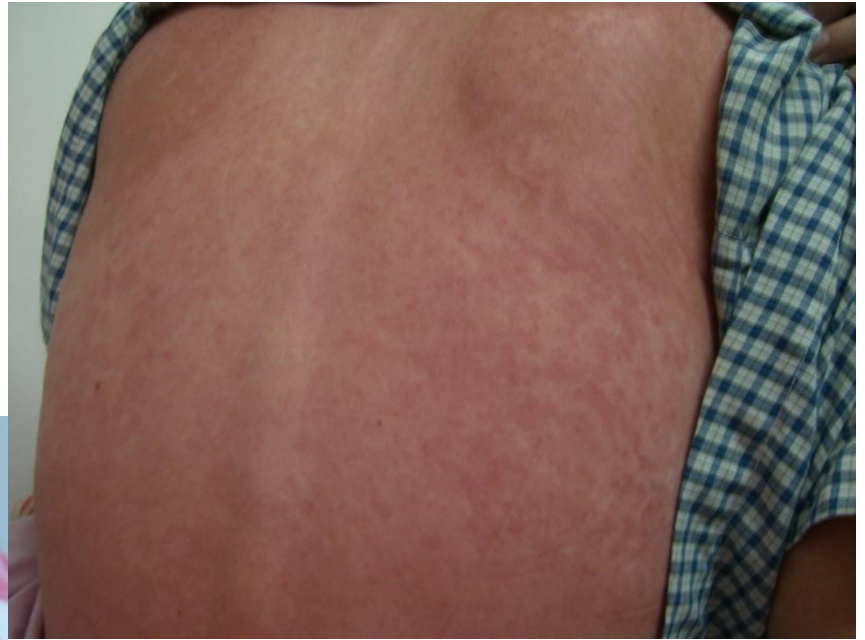
# Case 3

- 22 year old Dutch girl on “Noah’s Ark” with travels to Philippines, Cambodia, Kenya, Tanzania, Malaysia, Thailand, Rwanda and Nepal- travel started in September presented in April with fever and rash
- In Tanzania, had headache, diarrhea, nausea, fatigue, rash for 3 days, took 3 doses of ciprofloxacin with resolution
- Arrival from Rwanda 10 days before illness
- 4 days of headache, nausea, diarrhea and vomiting- seen at another hospital in Nepal - given ciprofloxacin

- 2 days later, admitted to yet another hospital for continuous watery diarrhea despite ciprofloxacin x 4 doses, with fevers and rash
- Rash started on trunk, spread to face/arms/legs/hands/feet- not pruritic
- Was short of breath requiring oxygen
- Transfer to CIWEC

# Exam

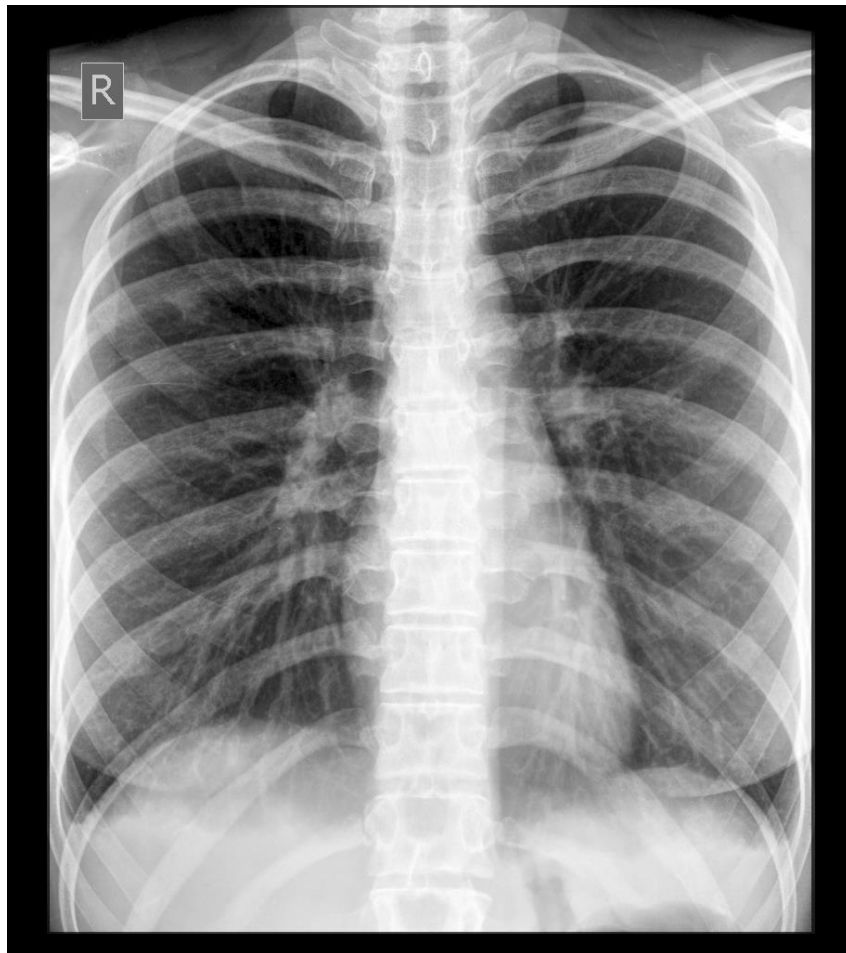
- Temp - 39.7C pulse -100/min, BP – 80/50mm
- Facial edema, conjunctival injection
- Pharyngeal erythema w/o pus
- Lungs- crepitations in both lungs> on right
- Abdomen - Mild tender hepatomegaly
- Skin- erythematous, maculopapular, blanching, rash, confluent over back and chest, palpable over distal digits



# Diagnositics

- Labs: WBC-8800/cu mm, platelet – 160K
- Bilirubin-1.3, AST- 356U/L, ALT- 157 U/L, Alk phos- 195
- Malaria rapid Ag test and smear negative
- Dengue IgM and antigen (NS 1) negative
- Stool – 2+ WBC's and mucus

# Chest Xray



# Causes of febrile rash in travelers

- Noninfectious causes: adverse drug reaction
- Viral: dengue, chikungunya, other arboviral infections, measles, rubella, HIV, Epstein – Barr Virus and cytomegalovirus primary infection, viral hemorrhagic fever
- Bacterial: rickettsial infections, typhoid fever, meningococemia (purpura), syphilis, rat-bite fever (*Spirillum minus*), leptospirosis, trench fever, brucellosis
- Parasitic infection: African trypanosomiasis, trichinellosis, toxoplasmosis



# Clinical Course

- Treated with IV fluids, oral doxycycline, ceftriaxone 2gms IV/day, paracetamol and Ibuprofen
- Also given oxygen and bronchodilators
- 1 d later T 40C (104 F), vomited black material – pantoprazole added, Hct stable
- WBC-9400 with 7% bands, decreased transaminases
- HBsAg, Anti HCV negative, Hep A and E pending, rickettsial/lepto serology pending
- Blood culture no growth in 24 hours

# Clinical Course

- Hep A IgM- negative
- Hep E IgM/IgG- negative
- Rickettsial, leptospire serology - negative
- Measles IgM antibodies strongly positive
  
- Improvement noted after 48 hours
- Much improved on day 5 of hospitalization
- Discharged to hotel on day 6
- Laboratory results came back on day 10

# Fever Returned Traveler from GeoSentinel [Wilson, 2007]

- Malaria, dengue, enteric fever, rickettsial
  - Oceania, Sub-Saharan Africa: malaria;
  - SE Asia: dengue
  - SC Asia: Enteric Fever (28% S paratyphi)
- Vaccine-preventable: Typhoid, acute Hep A, Influenza
- 12 deaths (malaria (4), acute HIV, ARDS, PE, angiostrongyloides, EBV, unspecified )
- VFRs: more vaccine-preventable [OR 1.8], more enteric fever (34% of enteric fever from SC Asia), less pretravel advice [OR 0.24]
- 22% “unspecified fever”

# CIWEC GeoS/Chart Data 5 years (2010-2015)

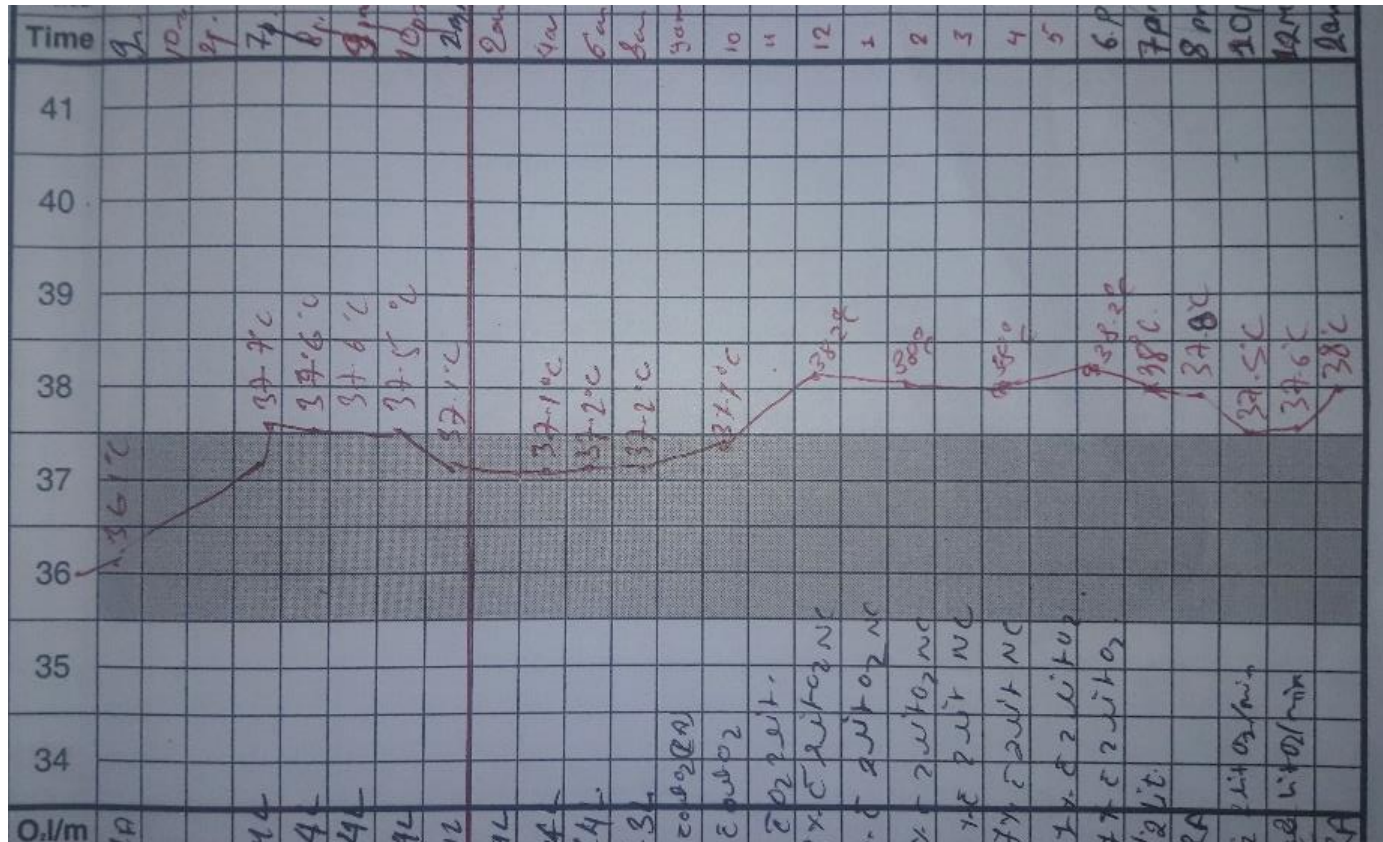
- 80 Enteric Fever: 19 *typhi* vs 58 *paratyphi* (73%)
- Dengue 42
- Influenza 40 (30 A vs. 10 B)
- Malaria 21
- Hepatitis A 11
- Measles 8
- Chikungunya 4
- Rickettsia 4
  
- Viral syndrome with fever 180
- Fever unspecified 65



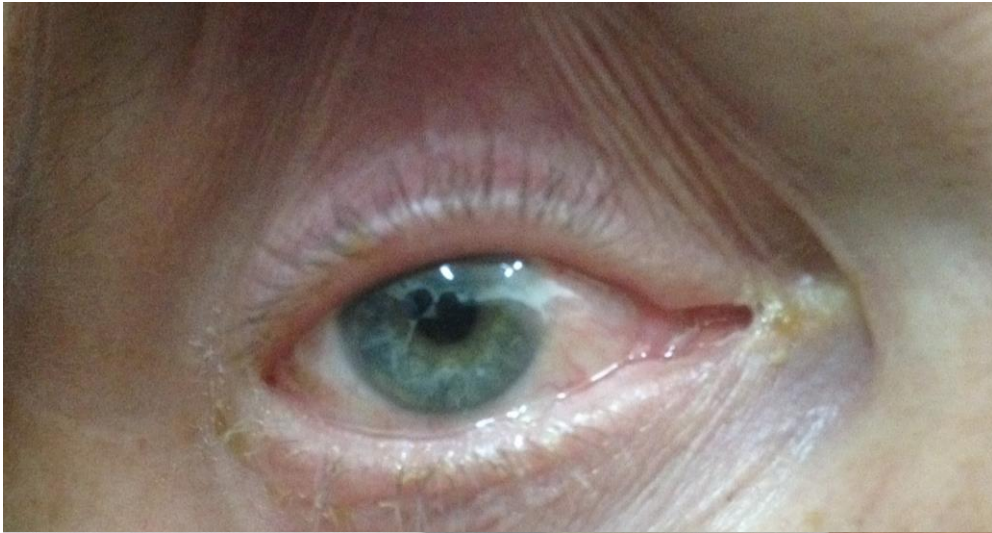
# Case 4. Fever and Rash

- 60 yo Norwegian orthopedic surgeon trekking in Annapurna region developed 8 days anorexia; 4 days high fever spikes  $>40$  C, “flu-like symptoms” with cough
- Evacuated by helicopter
- 3 episodes diarrhea, arrived with Temp 36; hypotensive 60/50; p 86
- Bil lung crackles; tender liver
- R wrist and bil ankle pain – taking 4g/day paracetamol w/o relief
- Total symptomatic period 16 days

# Fever Curve Day 1-2



# Rash, conjunctivitis

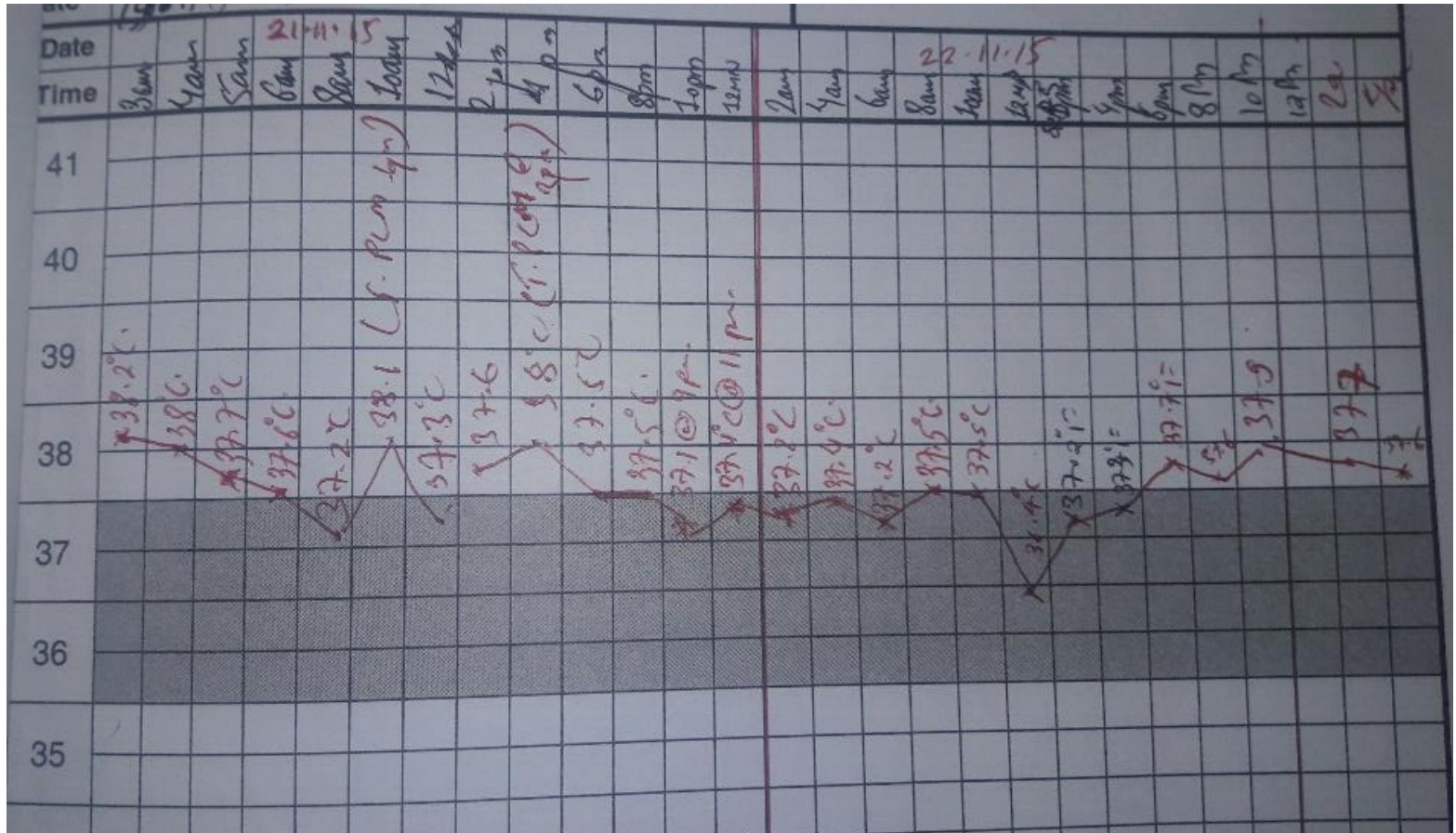




# Diagnostics

- AST 67; Creat 1.7; troponin neg
- Na 130
- CRP >120 mg/L
- WBC 8800 (2B; 90N; 7L; 1M); plt 103K
- Stool pus/mucous ++; few blastocystis; neg OP
- Urine blood +++; WBC 2, RBC 3; few granular casts
- Chest Xray RLL infiltrate

# Day 3-4 Fever Curve



# Clinical Course

- Ceftriaxone initially
- Required pressure support (noradrenaline) in ICU for first 3 days; decreased urine output; worsening rash and ankle pain
- Platelets drop to 28,000 associated with OP petechiae and conjunctival suffusion, nail beds with splinters
- 2D echocardiograph shows LVEF 45%; no vegetations seen



# Arthritis, rash



# Diagnostics

- Leptospira IgM, IgG negative
- Murine typhus, Scrub typhus, SFG neg
- Dengue (IgM/IgG) NS1 (Ag) neg
- Influenza neg
- Chikungunya neg
- Brucella IgM/IgG neg
- Mycoplasma IgM/IgG neg
- Urine legionella Ag neg

# Clinical Course

- 2 sites from initial blood draw with Group A Strep; amoxicillin R; amoxiclav sensitive
- Treated with IV amoxiclav; 2-D echo neg for vegetations x 2
- Medical evacuation to Norway for completion of care

# Case 5. Fever Returned Traveler

- 47 yo ER physician in Nepal July 27-Aug 14 with acute febrile illness upon return to US
- Bad case of jetlag with Fevers to 103, drenching night sweats
- Frontal HA, R eye pain (h/o iritis flares) w/o photophobia
- Vomiting x1 and diarrhea
- PMH: Asthma, HLA B27 +, recurrent anterior uveitis, psoriasis vs eczema



# Exposures

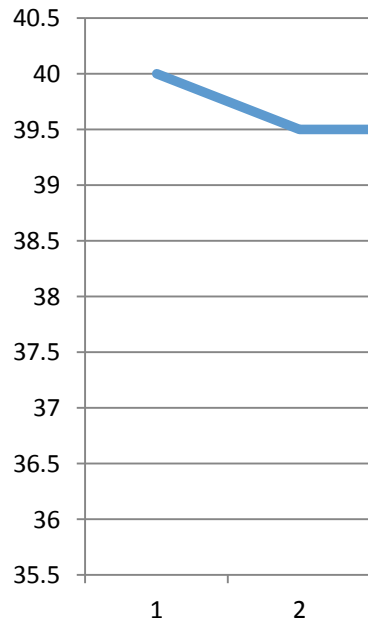
- Transit through Abu Dhabi
- 2 days after return from 2 week trip to Nepal; Pokhara, Lamjung (elev 1300 m) and Chitwan National Park, Bandipur
- *“Going Native”*: staying in local villages; contact with farm animals: goats, chicken, and water buffalo...exposures to untreated water and raw or uncooked foods and vegetables that may have been washed in untreated water.
- *...did not see any ticks, but did have exposure to leeches and mosquitos.*
- *...no overt sick contacts...no known exposure to blood or bodily fluids.*
- He has routine vaccinations for health-care associated illnesses. He was not on malaria or typhus prophylaxis during the trip

# “Going Native”



# Presentation with Fever Curve

- T 102 F; HR 81; RR 18; 100/63; SpO2 94RA
- No HSM, no rash

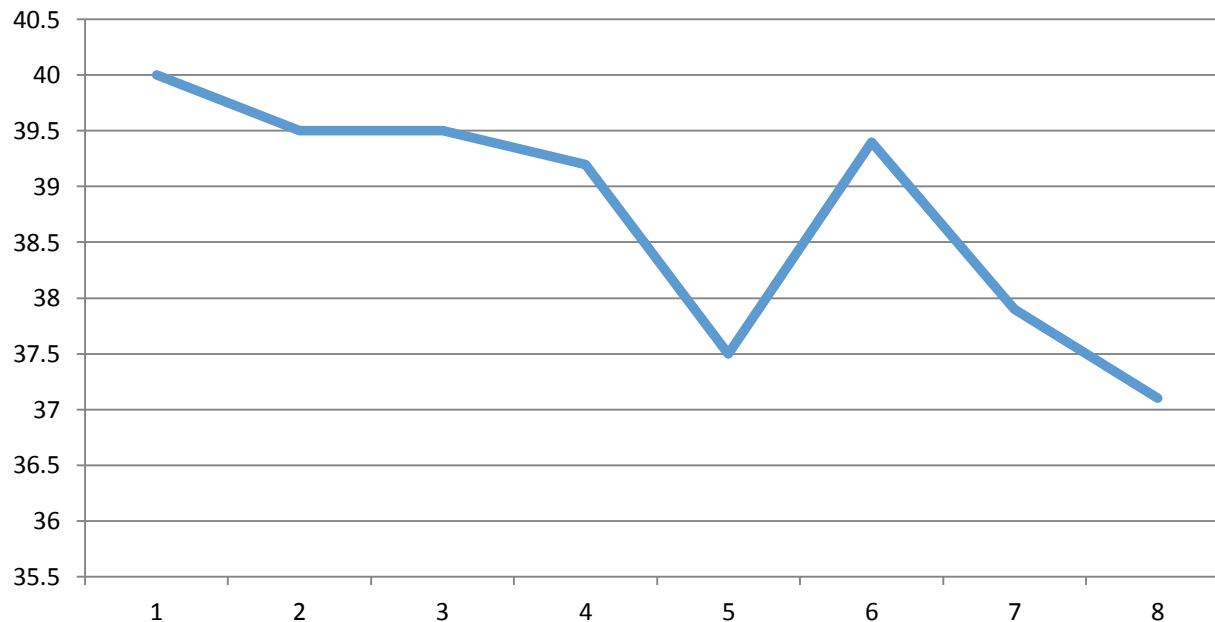


# Diagnostics

- ER visit 1: Aug 18- Na 138; creat 0.95; AST/ALT 55/42; CRP +; Plt 138,000; Abs Lymph 0.5; Hb 15
- ER visit 2: Aug 19 – AST/ALT 121/81; Na 132; plt 91,000; Abs Lymph 0.3; Hb 13.1
- Visit 3: Aug 20 – AST/ALT 244/245; Plt 57,000; Abs Lymph 0.7; Na 132

# Hospital Course

- Admit to ICU step-down unit; drenching sweats and with fevers daily, rigors; around the clock ibuprofen/paracetamol
- IV ceftriaxone, azithromycin, doxycycline



# Diagnostics

- Blood cultures (8/18; 8/19)
- Malaria smear
- Amoeba Ab
- Pinworm positive
- CXR (8/18): no acute process
  
- CXR (8/22):
  - Increased opacification of the right lower lung zone, concerning for developing airspace disease versus atelectasis.
  - Small right-sided pleural effusion.
  - Mild central vascular engorgement and interstitial edema.

# Diagnostics – CTPA 8/23

## IMPRESSION:

1. Widespread septal thickening, peribronchial cuffing, and patchy groundglass most suggestive of **moderate degree pulmonary edema**.
2. Additional **nodular component** also seen in both lungs with most measuring 5 mm or less, the largest measures 9 mm. These may indicate an additional component of underlying atypical infection. Followup over the next 2-3 months is advised to document improvement and exclude any underlying more ominous process.
3. Very mild apical paraseptal emphysema.
4. Mildly enlarged **bilateral hilar lymph nodes** may be reactive in nature.
5. Small bilateral pleural effusions and lower lobe atelectasis.
6. Bilateral perinephric stranding is a nonspecific finding. Correlation with renal function advised.

# CT Abd and TEE

1. Small bilateral pleural effusions with bibasilar atelectasis.
2. Mild hepatic steatosis.
3. Findings suggestive of **possible mild acute pancreatitis** involving the proximal pancreas. **Secondary inflammation of the duodenum.** Clinical correlation is advised.
4. Small amount of free fluid tracking in the abdomen pelvis, predominantly retroperitoneal. No loculated fluid collection identified.
5. No bowel obstruction.

Pericardial fluid (mild) with pericardial thickening



# Diagnostics

- Aug 21 – AST/ALT 179/200; Plt 34,000
- Aug 23 – AST/ALT 348/294; Plt 35,000; WBC 15,000
- Aug 24 – AST/ALT 145/185; WBC 18,000; plt 57,000
- Malaria smear neg x 2
- Dengue IgM neg/IgG pos
- Stool wbc +; O/P, culture, Cdiff neg
- Ebvca IgG + (IgM-)
- Legionella urine Ag neg
- Hanta virus PCR neg
- Leptospira IgM neg
- Blood cultures neg (Bactec) x 4 on first 2 days

# ? Enteric Fever

- Salmonella typhi Ab + (O type D and O type Vi)
- Salmonella paratyphi Ab + (h type and a)

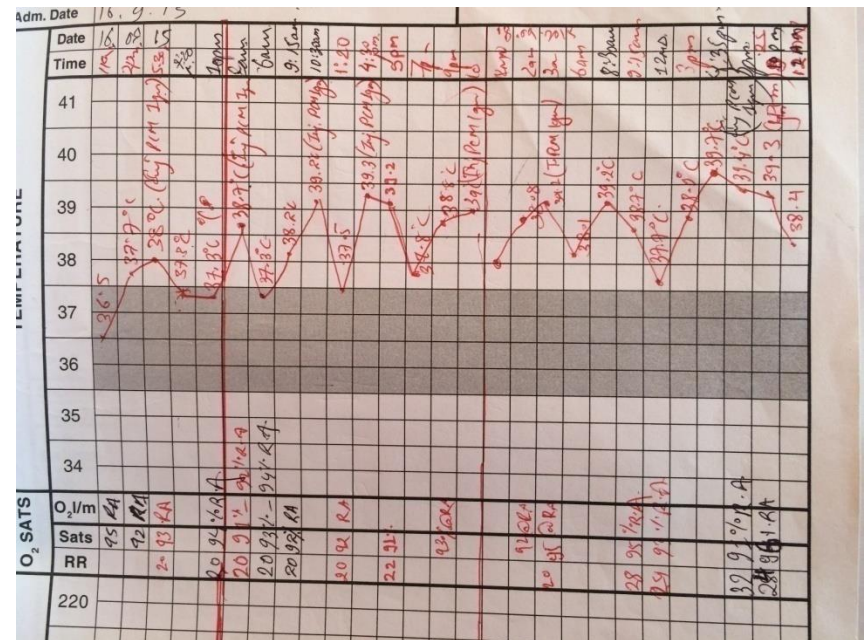


# Case 6. Cough, fever at altitude

- 64 year old American male fell 6 meters while doing Kanchenjunga base camp trekking
  - cough in Taplejung at the start of trekking
- Past history of nephrectomy due to malignancy; prostate cancer 2 years prior – finished with chemotherapy 5 months prior
- Developed dizziness, nausea and back pain
- Helicopter evacuation to Kathmandu after 5 days

# Clinical Presentation

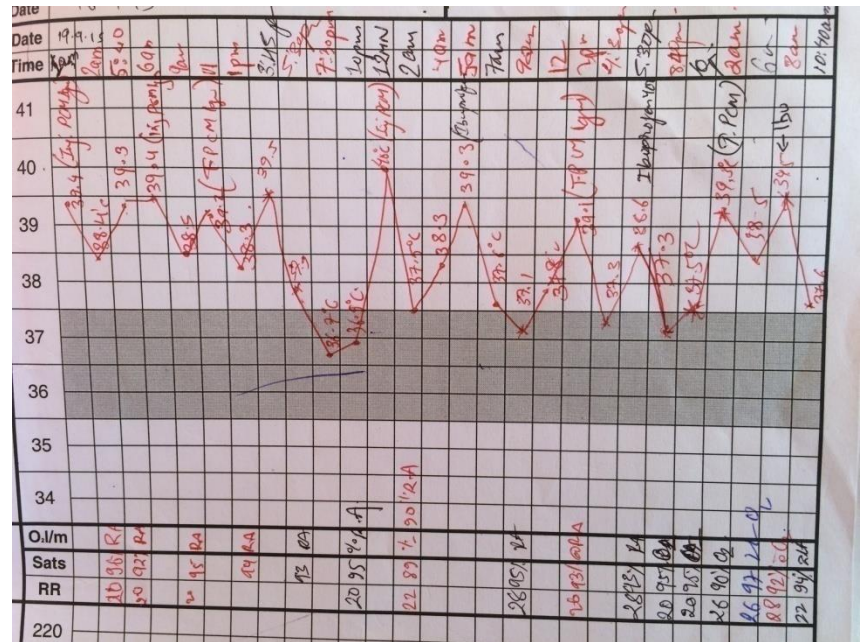
- Examination: unwell, T 36.5, BP- 100/70mm, P- 75/min Hg, SpO2 – 97%, tender right lumbar para-spinal region
- Started spiking temperatures over 39C



# Diagnostics

- WBC- 2,400/cumm, N-85, L-10, E-2, M-3,
- Platelets 97K, Hct-40.5%
- BUN/Creatinine- 16/1.7mg/dl
- Urinalysis, Liver function tests normal
- Admitted for pain control

- Swinging high temps every 4-6 hours
- Drenching sweats when temp came down
- Headaches and mild dry cough
- Marked fatigue



## Tests

- Dengue NS-1/IgM negative
- Malaria smear and rapid tests negative
- Rickettsial panel (rapid tests) negative
- Influenza rapid test negative
- CXR and Abdominal Ultrasound negative
- Leptospira antigen, Legionella urinary antigen negative
- Brucella IgM negative
- Blood cultures no growth
- CRP positive at 44mg/L



# Clinical Course

- Fevers started to abate after 10 days
- Weight gain of 10 Kg with edema up to groin – treated with intermittent diuretic, cardiac work up normal
- Intermittent drowsiness noted – normal MRI of brain
- On day 12, afebrile, diuresing and walking with walker
- Subclinical hypothyroidism noted TSH – 12.4
- Discharged on 16<sup>th</sup> day of admission – flew back to USA, non medical escort, business class and wheelchair assistance



**Neuroscience Centre for Research and Development**  
**WHO Collaborating Centre for Research and Training on Viral Zoonoses**  
**King Chulalongkorn Memorial Hospital, Bangkok**  
Research Development Service      Tel: (+66)2-256-4000 Ext. 3576, 3561

## REPORT

Name: [REDACTED]      **HN:** 5855149      **Reported:** 2/10/2558  
**Specimen:** Serum      **Ward:** AFRIMS      **Received:** 28/09/2558  
**Collection date:**      **Hospital:** CIWEC, Nepal

Lab No.	Test	Result	Internal Control	Method
UD306	Hantaviruses	Not detected	Valid	Conventional RT-PCR



**Neuroscience Centre for Research and Development**  
**WHO Collaborating Centre for Research and Training on Viral Zoonoses**  
**King Chulalongkorn Memorial Hospital, Bangkok**  
**Research Development Service      Tel: (+66)2-256-4000 Ext. 3576, 3561**

## REPORT

**Name:**       **HN:** 5855149      **Reported:** 5/10/2558  
**Specimen:** Serum      **Ward:** AFRIMS      **Received:** 28/09/2558  
**Collection date:**      **Hospital:** CIWEC, Nepal

Lab No.	Test	Result	Internal Control	Method
UD306	Flaviviruses	Not detected	Valid	Conventional RT-PCR

# REPORT

Name:

HN: 5855149

Reported: 5/10/2558

Specimen: Serum

Ward: AFRIMS

Received: 28/09/2558

Collection date:

Hospital: CIWEC, Nepal

Lab No.	Test	Result	Internal Control	Method
UD306	Mycoplasma pneumoniae	Not detected	Valid	multiplex PCR
	Legionella pneumophila	Not detected	Valid	multiplex PCR
	Streptococcus pneumoniae	Not detected	Valid	multiplex PCR
	Haemophilus influenzae	Not detected	Valid	multiplex PCR
	Bordetella pertussis	Not detected	Valid	multiplex PCR
	Chlamydophila pneumoniae	Not detected	Valid	multiplex PCR

**Neuroscience Centre for Research and Development**  
**WHO Collaborating Centre for Research and Training on Viral Zoonoses**  
**King Chulalongkorn Memorial Hospital, Bangkok**  
Research Development Service      Tel: (+66)2-256-4000 Ext. 3576, 3561

## REPORT

**Name:**       **HN:** 5855149      **Reported:** 5/10/2558  
**Specimen:** Serum      **Ward:** AFRIMS      **Received:** 28/09/2558  
**Collection date:**      **Hospital:** CIWEC, Nepal

Lab No.	Test	Result	Internal Control	Method
UD306	Severe fever with thrombocytopenia syndrome virus (SFTSV)	Not detected	Valid	Qualitative real-time RT-PCR (1)
	Crimean-Congo hemorrhagic fever virus (CCHF)	Not detected	Valid	Qualitative real-time RT-PCR (2)

# “Andrus Fever”

- Unknown fevers – about 10 traveler/expats per year, mainly trekkers with rural exposure
- Syndrome of high fevers, leucopenia, thrombocytopenia, third spacing of fluids (capillary leak syndrome), marginal BP, hypoxemia requiring oxygen, recovery after about 10 days
- Suspect viral etiology – still remains unknown

# Undifferentiated febrile illness in Nepal

- 627 patients with fevers (34.8% Enteric fever)
- Stored sera on 125 patients tested
  - Murine typhus 21 patients
  - Hanta virus in 2 patients
  - Q fever in 1

# Diagnostic Conundrums

- Sampling times: acute, 2-week convalescent, 4-6 week convalescent
- Store -20 C or colder (ideally -70)
  - Sample storage/transport
- Role for lumbar puncture
  
- During-After Travel collaborations
- “biobank”
- [www.fevertravel.ch](http://www.fevertravel.ch)



# Clinical conundrums

- Atypical presentations vs recognizing a “typical” fever curve?
- Atypical pathogens
  - Recognizing vector/pathogen evolution
- Antibiotic resistance
  - Improving data from the “tropics”
  - Addressing Antibiotic Resistance
  - Appropriate use of Antibiotics

# Management conundrums

- When to broaden antibiotics?
- When to narrow antibiotics?
- Azithromycin vs. doxycycline vs. both?
- Evacuation

Thank you for your endurance

