Citywide Conference

HoJoon You, MD PGY-4

Case

Chief Complaint:
Sudden onset of stumbling and slurred speech

HPI:

60’s old Male who presented to the ED after being found unsteady on his feet at home with slurred speech the night of his presentation.

History

Medical Hx:

- HTN
- Diabetes
- BPH
- ESRD
- Alcoholic/HCV cirrhosis s/p Kidney/liver transplant (4 month ago)

Allergies:

NKDA

Social History:

- Former Smoker for 15years
- Former alcohol use
- No illicit drug use
- Lives with spouse
- Independent with all ADLs, ambulates with cane at baseline
- No recent travel

Additional History

- Recent hospitalization for neutropenia and shortness of breath. He was ultimately found to have a large right-sided pleural effusion. Thoracentesis was negative for infection or malignancy.

Medications

Bactrim 400 mg-80 mg daily
CellCept 1000 mg q12 hours
Harvoni 90 mg-400 mg daily
prednisone10 mg daily
Prograf 1 mg q12 hours
tacrolimus 5 mg q12 hours
Valcyte 450 mg daily

aspirin
Coreg
docusate-senna
Flomax
insulin lispro
Lantus Solostar Pen
magnesium oxide
NIFEdipine
patiromer
Vitamin D3
Zantac

Physical exam

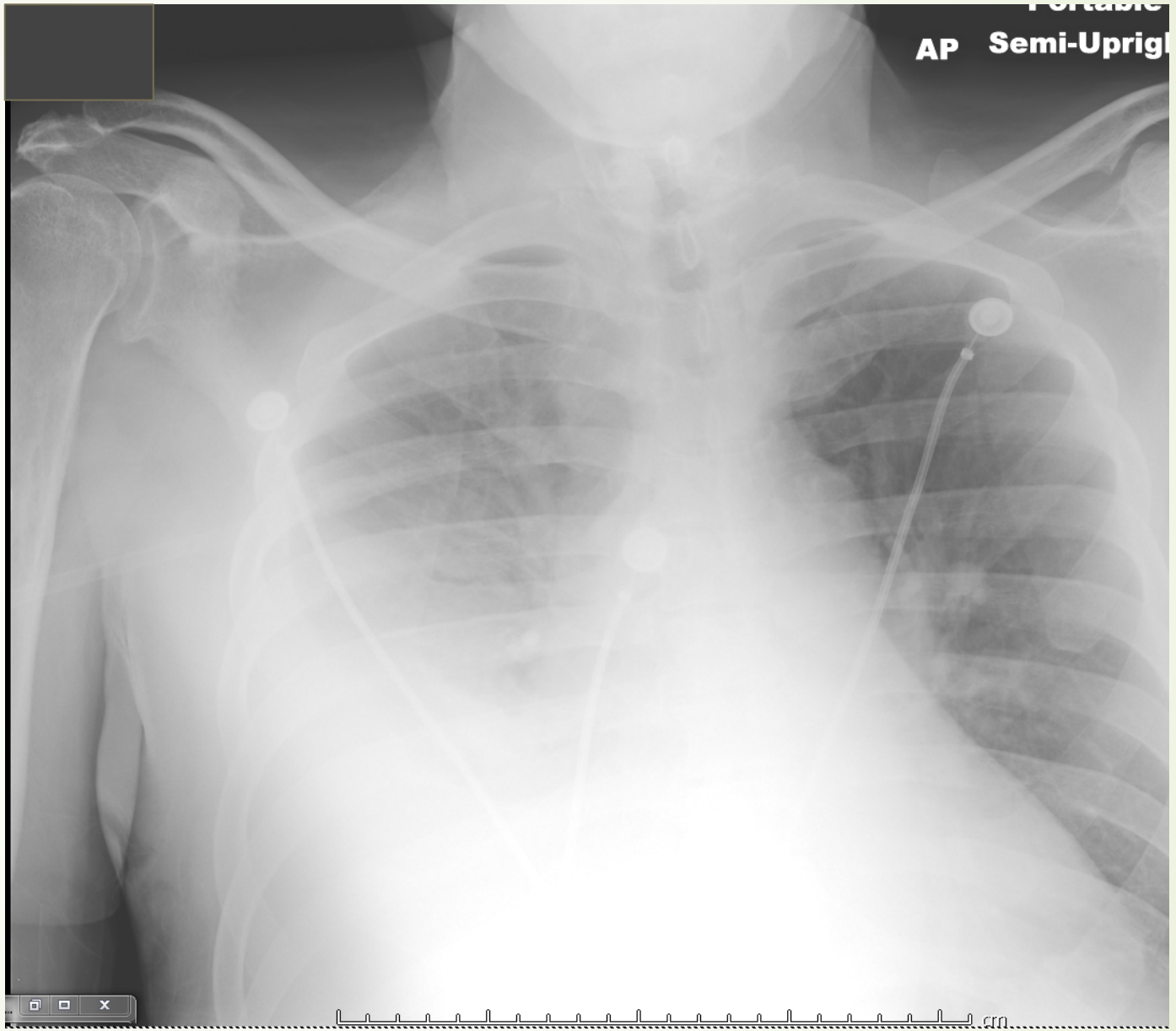
- Vitals: T 39.2 C HR 104 BP 152/81 RR 24 Pox 89% RA
- General: Elderly male in NAD but tremulous. Awake but unable to answer any questions appropriately. Unable to state his name or follow commands
- Eye: PERRL, EOMI, white sclerae
- Neck: No lymphadenopathy, supple
- Respiratory: Bronchial breath sounds over the right chest wall. Left chest CTA
- Cardiovascular: Regular, tachycardic
- Gastrointestinal: Soft, Non-tender, non-distended, normal bowel sounds. Postsurgical scars well healed over the epigastrium and right iliac fossa
- Genitourinary: No penile lesions or drainage
- Integumentary: No lesions or rash appreciated
- Neuro: CN intact but unable to formally test
  Motor – Coarse resting tremors of the upper and lower extremities
  Sensory - intact

Labs

- WBC 11.5 (N^{64} L^{16} M^{14} E^{0})
- Hgb/Hct 9.9/33.5
- Plt 271
- BUN/CR 29/1.5
- LFTs WNL
- UA: Neg nitrites, 0-5 WBC, 5-10 RBC

Imaging

CXR



Imaging (cont…)

CT head w/o contrast:

- No intracranial hemorrhage
- Chronic lacunar infarction along the anterior limb of the right internal capsule.
- Parenchymal volume loss and sequela of chronic small vessel ischemic change.

Imaging (cont..)

CT chest/abd/pelvis w/ contrast

- No intestinal obstruction
- Right sided pleural effusion
- Right sided ascites
- Postsurgical changes s/p orthotopic liver transplant and right iliac fossa kidney transplant.

Hospital course

- He was given empiric vancomycin, cefepime, and Flagyl in the ED.
- He remained febrile and with increasing respiratory distress and so ID was consulted regarding the persistent fevers
- The patient remained stuporous and underwent IR guided thoracentesis and lumbar puncture. His antibiotic regimen was changed to Vancomycin, Ampicillin and Ceftriaxone for meningitis

Lumbar Puncture

- 308 WBC
- <1000 RBC
- 69% segs
- 26% lymphs
- 5% mono
- 105 glucose (serum glucose 215)
- 192.1 protein

Thoracentesis

- WBC 511
- RBC 1000
- Seg 16%
- Lymph 43%
- Mono 24%
- LDH 214
- Protein 4.1

Hospital Course (cont...)

- Patient continued to have myoclonic jerks prompting Neurology to start anti-epileptic medications as EEG had evidence of some epileptiform activity
- A Lumbar puncture was repeated to obtain more CSF to send for a meningoencephalitis panel
- Patient was started on steroids for possible inflammatory encephalitis from a recent filgrastim administration

Discussion

- Questions
- Differentials
- Thoughts

Labs

Meningoencephalitis panel

- HSV 1 and 2 IgG and IgM positive
- WNV IgG and IgM Positive
- Negative antibodies to remainder of panel

Thoracentesis was negative for culture growth and AFB

West Nile Virus

Typically a self-limiting illness transmitted by mosquitos but there have been cases of donor derived WNV in solid organ transplant patients.

From these small number of cases, it appears that there is an increased incidence of neuroinvasive disease with a median onset of symptoms about 13 days after transplantation (Range of 5-37)

R.J. Nett, M.J. Kuehnert, M.G. Ison, J.P. Orlowski, M. Fischer, J.E. Staples. Current practices and evaluation of screening solid organ donors for West Nile virus. Transpl Infect Dis 2012: 14: 268–277.

Winston DJ, Vikram HR, Rabe IB, Dhillon G, Mulligan D, Hong JC, Busuttil RW, Nowicki MJ, Mone T, Civen R, Tecle SA, Trivedi KK, Hocevar SN, West Nile Virus Transplant-Associated Transmission Investigation Team. Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. Transplantation. 2014 May;97(9):881-9.

West Nile Virus

Neuroinvasive disease with WNV presents as a fever with meningitis, encephalitis, flaccid paralysis or a mixed pattern

Other neurological deficits can include brachial plexopathy, demyelinating neuropathy, motor axonopathy, axonal polyneuropathy, Ventral spinal root involvement, myasthenia gravis and a Guillain-Barre like syndrome

West Nile Virus

Positive HSV-1 and 2 IgG and IgM but negative HSV 1 and 2 PCR
Positive WNV IgG and IgM
Possible cross-reactivity?

HSV 1 and 2 Immunoglobulins reported to have cross reactivity with VZV and CMV

Thedi Ziegler, Olli Meurman, Tuula Lindholm, Guido Scalia. Causes of false-positive reactions in herpesvirus IgM assays, In Serodiagnosis and Immunotherapy in Infectious Disease, Volume 3, Issue 2, 1989, Pages 101-109, ISSN 0888-0786

West Nile Virus

MAC-ELISA for WNV is known to have false positives in the setting of the presence of other flaviviruses

Dengue virus

Tick-borne encephalitis virus

yellow fever virus

Zika virus

Japanese encephalitis virus serocomplex

St. Louis encephalitis

D.A. Martin, B.J. Biggerstaff, B. Allen, A.J. Johnson, R.S. Lanciotti, J.T. Roehrig. Use of Immunoglobulin M Cross-Reactions in Differential Diagnosis of Human Flaviviral Encephalitis Infections in the United States. Clin Diagn Lab Immunol. 2002 May; 9(3): 544–549.

CDC criteria for laboratory diagnosis of WNV

Confirmed case

- Isolation of virus, specific viral antigen or nucleic acid in tissue, blood, CSF or other body fluid OR
- Fourfold or greater change in virus-specific quantitative antibody titers (Plaque reduction neutralization test) in paired sera OR
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies (PRNT) in the same or later specimen OR
- Virus specific IgM antibodies in the CSF and negative IgM in the CSF for other arboviruses endemic to the region

https://wwwn.cdc.gov/nndss/conditions/arboviral-diseases-neuroinvasive-and-non-neuroinvasive/case-definition/2015/

Thank You

Citywide: Nov 2017

Gokul Yaratha

HPI

- 30’s yo Chinese Lady w/ no significant PMHx whom was admitted in June for fevers and chills
- 3 days prior to admission, developed
  - Daily intermittent fevers up to 39C with no appreciable pattern
  - Body aches in the lower back and shoulders
  - Intermittent chills, no rigors
  - Nausea
  - Anorexia during the course of her illness

HPI

- 1 week PTA, she had returned from a 3 month trip to Myanmar
  - Resided only in Yangon with her family
  - Received no Malaria PPX or vaccinations prior to her travel
  - Reported no illness while in Myanmar
    - Father reportedly diagnosed with Malaria in May
  - Denied eating abnormal foods, other sick contacts, or exposures to animals
  - Thinks she may have had several mosquito bites while in Myanmar

HPI

- Denied leaving home, sick contacts, eating abnormal foods, or exposures upon return to the US.
- ROS Neg:
  - Sore throat, rhinorrhea
  - Cough, Chest Pain or SOB
  - Mastalgia nor change in the color of consistency of her breast milk
  - Abdominal pain, vomiting, diarrhea, flank pain or urinary symptoms,
  - Arthralgias or joint pain.

HPI

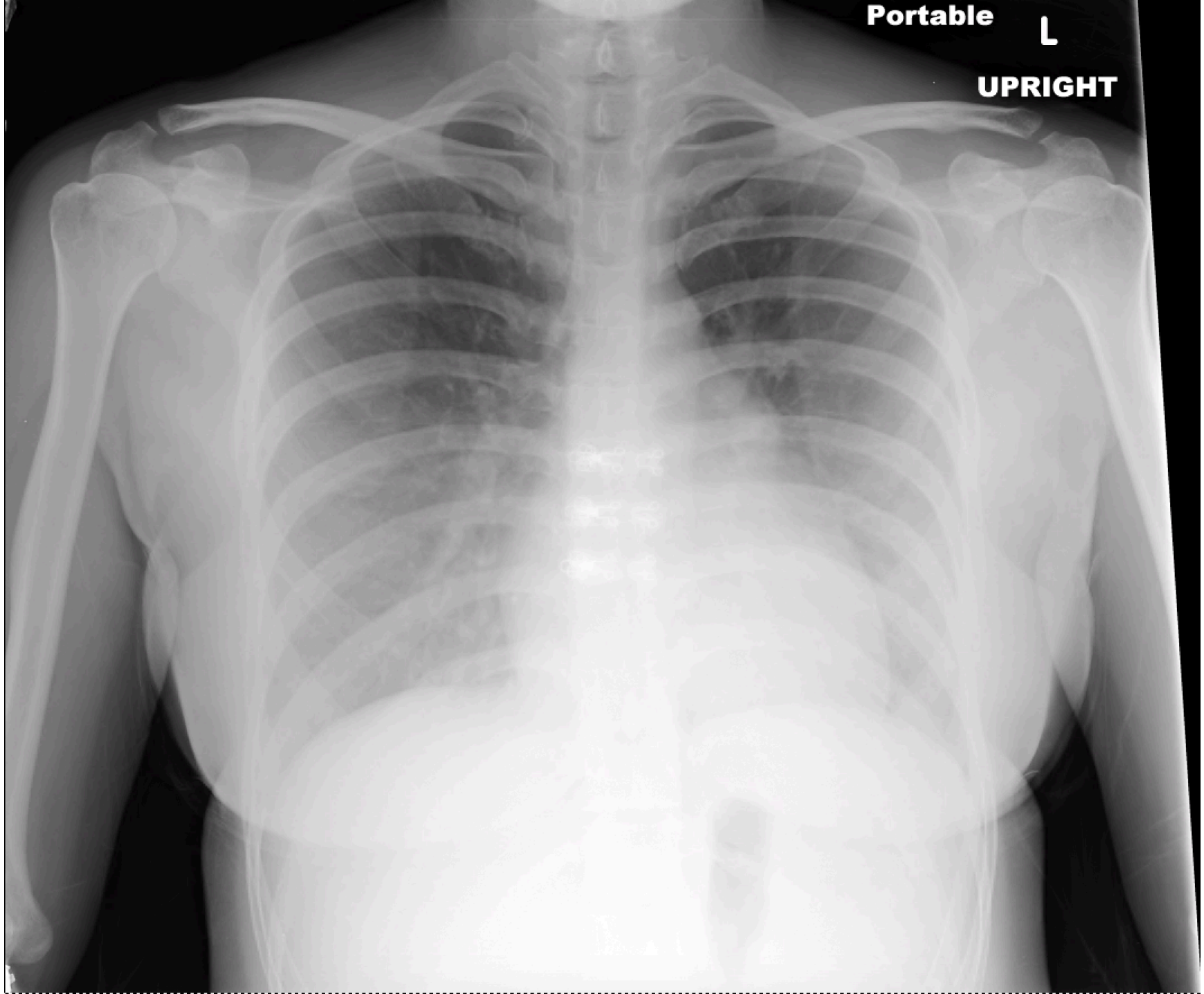
- PMHx: None.
- Allergies: NKDA
- Medications: No regular medication usage
- Surgical History: None
- GYN: G1P1001. Delivered health baby boy in one year ago via SVD w/o any peri-partum complications. Currently breastfeeding.
- FMHx: CAD and DM2 in Father. Mother had hypothyroidism. 2 younger siblings w/o any medical conditions. Son was healthy.
- Social: No history of any toxic habits. Housewife. In monogamous relationship with husband. Lived near the hospital in a suburban area with her husband and son w/ no pets.

Physical Exam

- **VS: T39.5 P88 BP 111/64**
- **GEN: AOx3, In NAD**
- **HEENT: PEERLA. No conjunctival suffusion. Oral mucosa moist w/ no lesions. No thrush. Supple Neck**
- **CV: S1,S2+ No M/R/G**
- **Lungs: CTABL**
- **AB: Soft, NT, ND, BS+. No RUQ, suprapubic, or CVA tenderness. No appreciable organomegaly**
- **Extremities: No edema in LE. No swelling or effusions w/ normal ROM in the joints of the hands, shoulders, and knees B/L**
- **LN: No appreciable LAN in the cervical, axillary, or inguinal region**
- **SKIN: Normal turgor, no rash**

Labs

- Na 139 K 3.2 CL 103 CO: 26 BUN 10 Creat: 0.7
- ALP: 29 TB: 0.4 DBil 0.1 Alb 3.7 **AST 59 ALT 47**
- **WBC: 2.5 (ANC 1.5, B 37%, Abs. Lymph 0.8)** H/H 12.0/36.3 **PLT: 69**
- UA: 0-5 WBC
- HIV: Negative
- Malaria Smear x 1: NEG
- Blood Cultures x 2: PND, UCx: PND


Portable
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UPRIGHT

DDX

Further Diagnostics

RX

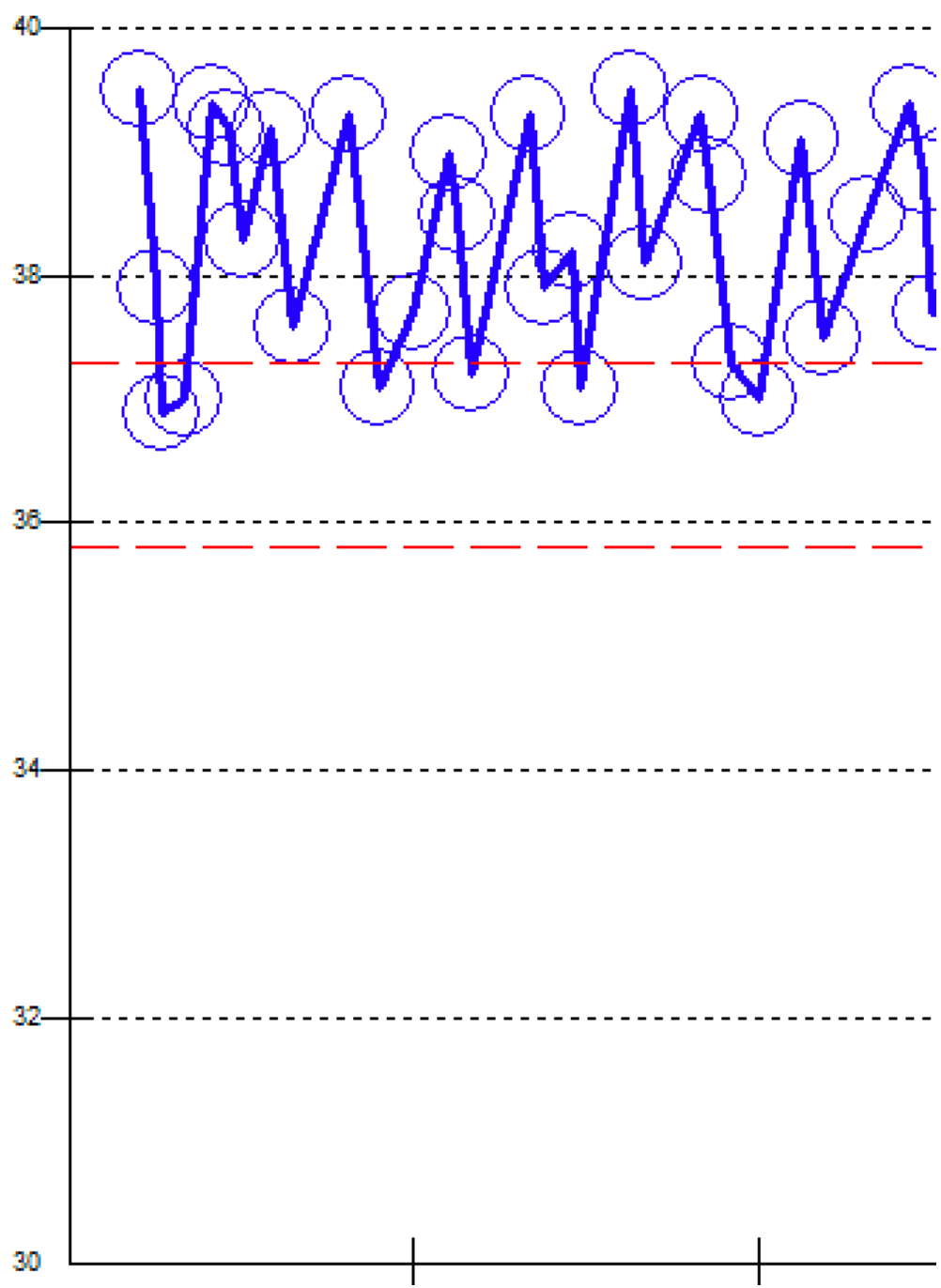
Hospital Course

- Admitted to GMF
- No ABx given initially

- ID C/S
  - Repeat Malaria Smear x 2 w/ BiNAX
  - Check Dengue and Zika Serology
  - Continue supportive care

Hospital Course

- Initial Blood and Urine Cultures: Negative
- Malaria Smear NEG x 2
  - BiNAX negative
- Continued to remain febrile for following 3 days w/o any new symptoms.
- Labs remained unchanged
  - Mild transaminitis
  - Persistent Leukopenia, Unchanged Thrombocytopenia, Normal Coags
- Repeat blood cultures obtained on day 4 of fevers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Next Step?

Further Diagnostics

RX

How would your recommendations change once you found out repeat blood cultures obtained on D4 grew Gram Negative Rods

Hospital Course

- Fevers persisted through D4 of hospitalization
- Began to develop loose, non bloody diarrhea w/o any associated, nausea, vomiting, or abdominal pain.
- ID C/S
  - Stool studues
    - Culture
    - O&P
    - Stool for wet mount
  - CT A/P

Hospital Course

- W/U for etiology of fever
  - Dengue IgM: Neg
  - Zika RT-PCR from Urine and Blood: Neg
  - Stool studies
    - O&P: Neg
    - Wet Mount: No larvae seen
    - No stool culture sent
  - CTAP: Splenomegaly

Would you repeat or is there any clinical utility to repeating blood cultures at this point?

Sustained…GNR Bacteremia?

- Repeat cultures are routinely obtained for gram negative bacteremia
- Frequently asked if we should repeat blood cultures for gram negative bacteremia
- Evidence?

Sustained…GNR Bacteremia?

- Follow-up Blood Cultures in Gram-Negative Bacteremia: Are They Needed? *Clin. Infect Dis. 2017 Dec 1*

- Retrospective chart review of 500 episodes of bacteremia of which 378 had follow up blood cultures (FUBC).
  - Risk Factors for Persistent Bacteremia (+ cultures for same organism 24 hours after initial BC)
  - Frequency of FUBC

Sustained…GNR Bacteremia?

Table 1. Characteristics of Patients With Follow-up Blood Cultures (n = 383)

Characteristic	No. (%)
Male sex	211 (55)
Age, y, mean ± standard deviation	53 ± 15
Known source of bacteremia	273 (71)
Medical (vs surgical) disease	314 (82)
Initial bacteremia caused by	
Gram-positive cocci	206 (53.8)
Gram-negative bacilli	140 (37)
Polymicrobial	30 (8)
Gram-positive bacilli	6 (1.6)
Anaerobes	1 (0.3)
Patients on antibiotics the day of FUBC	347 (91)
Microorganism sensitive to those antibiotics	325 (85)
Fever on the day of FUBC	127 (33)
Presence of an IV central line	165 (43)
Presence of a bladder catheter or nephrostomy	119 (31)
Neutropenia (ANC < 1000/mL)	36 (9)
Diabetes mellitus	230 (60)
AIDS	28 (7)
ESRD on hemodialysis	92 (24)
Liver failure	53 (14)
Need for ICU care	165 (43)
In-hospital death	52 (14)

Sustained…GNR Bacteremia?

Table 2. Differences Between Patients Whose Follow-up Blood Cultures Were Positive or Negative

Characteristic	Positive (n = 55)		Negative (n = 328)		*P* Value
On antibiotics when cultures drawn	54	98%	312	95%	.49
Medical disease (vs surgical)	49	89%	265	81%	.18
Fever when cultures drawn	27	49%	100	30%	**.008**
Presence of a urinary catheter	11	20%	82	25%	.50
Presence of an IV central catheter	34	62%	121	37%	**<.001**
Neutropenia (ANC <1000/mL)	4	7%	29	9%	1.00
Diabetes mellitus	31	56%	121	37%	.19
HIV positive	3	5%	20	6%	1.00
ESRD on hemodialysis	24	44%	65	20%	**<.001**
Liver cirrhosis	5	9%	33	10%	1.00
ICU care required	18	33%	119	36%	.65
Death	3	5%	35	11%	.33

Sustained…GNR Bacteremia?

Table 3. Differences Between Patients Whose Follow-up Blood Cultures Were Negative, or Positive for Gram-Positive Cocci and Gram-Negative Bacilli

Characteristic	Negative (n = 328)		FUBC Positive for GPC (n = 43)		*P* Value[a]	FUBC Positive for GNB (n = 8)		*P* Value[a]
On antibiotics when cultures drawn	312	95%	42	98%	.71	8	100%	1.00
Medical disease (vs surgical)	265	81%	39	91%	.14	6	75%	.65
Fever when cultures drawn	100	30%	21	49%	**.02**	6	75%	**.01**
Presence of a urinary catheter	82	25%	9	21%	.71	1	13%	.69
Presence of an IV central catheter	121	37%	27	63%	**.002**	5	63%	.16
Neutropenia (ANC < 1000/mL)	29	9%	3	7%	1.00	1	13%	.53
Diabetes mellitus	121	37%	23	53%	**.04**	6	75%	.06
HIV positive	20	6%	3	7%	.74	0	0%	1.00
ESRD on hemodialysis	65	20%	20	47%	**<.001**	3	38%	.21
Liver cirrhosis	33	10%	3	7%	<.78	2	25%	.20
ICU care required	119	36%	12	28%	.31	4	50%	.47
Death	35	11%	3	7%	.60	0	0%	.36

Sustained…GNR Bacteremia?

Table 4. Incidence of Bacteremia per Source (n = 273)

Characteristic	No.	Positive		Negative		*P* Value
Urinary tract infection	71	2	3%	69	97%	**.001**
Severe skin infection	70	4	6%	66	94%	**.026**
Intravenous catheter	61	21	34%	40	66%	**<.001**
Pneumonia	34	5	15%	29	85%	.79
Intra-abdominal infection	21	2	10%	19	90%	.75
Endocarditis	6	1	17%	5	83%	.59
Osteomyelitis	5	0	0%	5	100%	1.00
Pleural empyema	3	1	33%	2	67%	.35
Septic arthritis	1	1	100%	0	0%	.14
Tonsillitis	1	0	0%	1	100%	1.00

Sustained…GNR Bacteremia?

- Persistent Bacteremia
  - Fever only risk factor a/w with positive repeat blood cultures
  - + FUBC more common w/ GPC
    - ESRD
    - IV Central Lines
  - + FUBC had no impact in mortality or morbidity
  - Small study limited clinical scenarios most commonly seen in the hospital

Would you repeat or is there any clinical utility to repeating blood cultures at this point?

Hospital Course

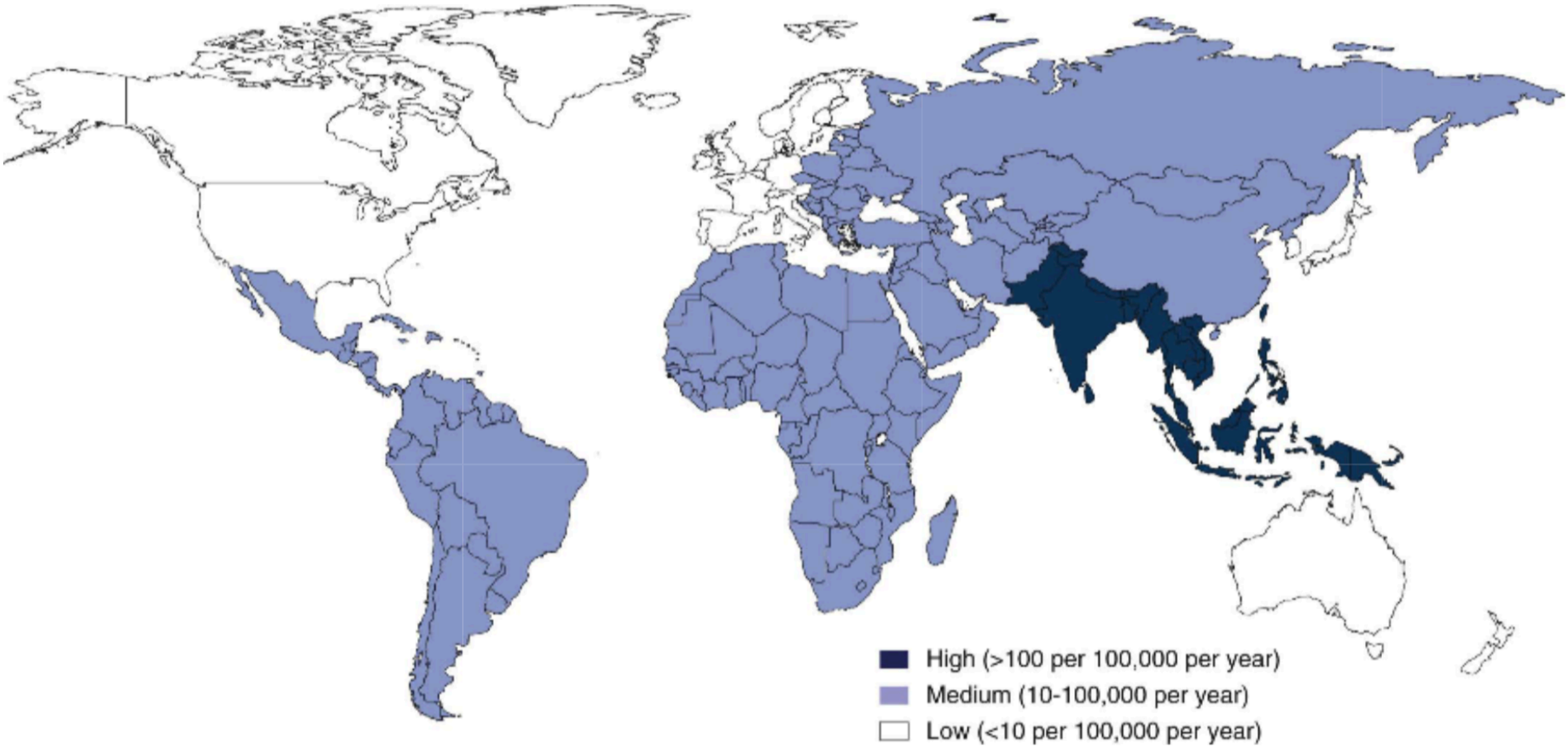
- W/U for etiology of fever
  - Dengue IgM: Neg
  - Zika RT-PCR from Urine and Blood: Neg
  - Stool studies
    - O&P: Neg
    - Wet Mount: No larvae seen
    - No stool culture sent
  - CTAP: Splenomegaly
  - Repeat Blood Cultures before ABx: GNR

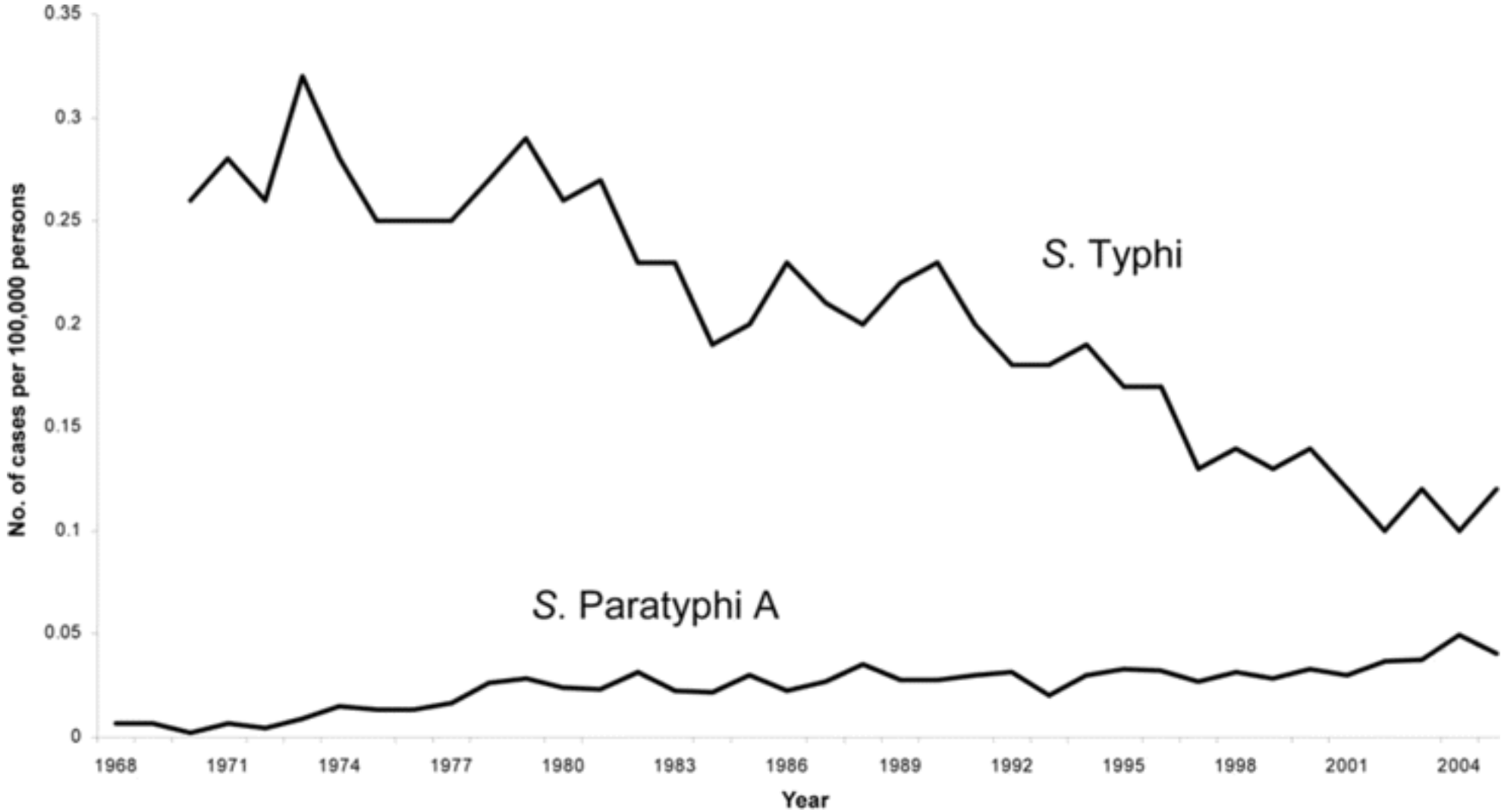
Diagnosis?

Hospital Course

- Initial Blood Cultures: Presumptive Salmonella

- Based on her presentation and travel history, can we make any presumptions about the specific etiological agent (S. typhi vs paratyphi) would be and are there any clinical implications?


High (>100 per 100,000 per year)
Medium (10-100,000 per year)
Low (<10 per 100,000 per year)



Incidence of infection due to *Salmonella* serotypes Typhi and Paratyphi A, 1968–2005, National *Salmonella* Surveillance System

Clinically Distinguishable?

- Salmonella enterica Serovar Paratyphi A and S. enterica Serovar Typhi Cause Indistinguishable Clinical Syndromes in Kathmandu, Nepal. *Clin Infect Dis. 2006 May 1*
  - 6 month Prospective study of 609 cases of enteric fever
    - 200 isolates were S. Paratyphi A
  - Clinically indistinguishable
    - Symptoms
    - Physical Findings
      - Wheezing more common S. typhi (14 (3.4%) vs 1 (0.5%) p = 0.03%)
  - Clinical outcomes similar between S. typhi and S. paratyphi
    - Complication Rates 5.65% vs. 3.5%; p = .2
    - Hospitalization Rates 5.4% vs 3%; p = .08
    - No fatalities in either group
  - Resistance between S. typhi and S. paratyphi
    - Lower FQ resistance: 50.5% vs 75.25%; p = <0.001%
    - Lower MIC: (0.38 vs 0.75; p= <0.001

Hospital Course

- Initial Blood Cultures: Presumptive Salmonella

- Based on her presentation and travel history, can we make any presumptions about the specific etiological agent would be and are their any clinical implications?

- Based on speciation of the GNR and her recent travel history, what would your initial antibiotics recommendations be or would they change?

Resistance Patterns in Enteric Fever Isolates

- Susceptibilities
  - In-Vitro, susceptible to variety of ABx
  - In-Vivo responses not reliably predictable
    - D/T Intracellular nature of organism
- Traditional First Line Agents
  - Chloramphenicol
    - First recognized in ~1950s
    - Resistance Detected in early 1970s
  - Aminopenicillins/TMP-SMX
    - Similar Efficacy to Chloramphenicol
    - Widespread resistance began to develop in the 1990s

Resistance Patterns in Enteric Fever Isolates

- MDR: Resistance to Chloramphenicol, TMP-SMX, and Aminopenicillins

- Rise of MDR led to shift to usage of predominantly FQ ~ 20 years
  - Increase in FQ resistance
    - Some areas with ~80% resistance
  - Increase in FQ usage led to decrease in MDR isolates

Resistance Patterns in Enteric Fever Isolates

- Changing Patterns in Enteric Fever Incidence and Increasing Antibiotic Resistance of Enteric Fever Isolates in the United States, 2008–2012. *Clin Infect Dis. 2016 Aug 1*

- Retrospective study looking at incidence and resistance patterns of S. typhi and parathyphi A isolates in the US from 2008-2012

- 2341 cases of enteric fever reported to CDC
  - ~80% Typhoid
  - ~20% w/ Parathyphoid A
    - Incidence increased in study period mimicking current trends

Resistance Patterns in Enteric Fever Isolates

- 86% of patients reported foreign travel within preceding 30 days
  - Travel to SE Asia most common
    - 82% of isolates for S. Typhi
    - 97% of isolates for paratyphoid A
- Resistance
  - ~65% of S. typhi isolates were resistant to Naldixic Acid (NAL-R)
  - ~93% of S. paratyphi isolates were NAL-R

Resistance Patterns in Enteric Fever Isolates

- MDR
  - 12% of isolates were MDR; limited to S. Typhi
    - Most were acquired from South East Asia
  - Most MDR isolates were NAL-R
- No resistance to Ceftriaxone, Azithromycin
- No ESBL producing isolates
  - C/W current trends of resistance

Hospital Course

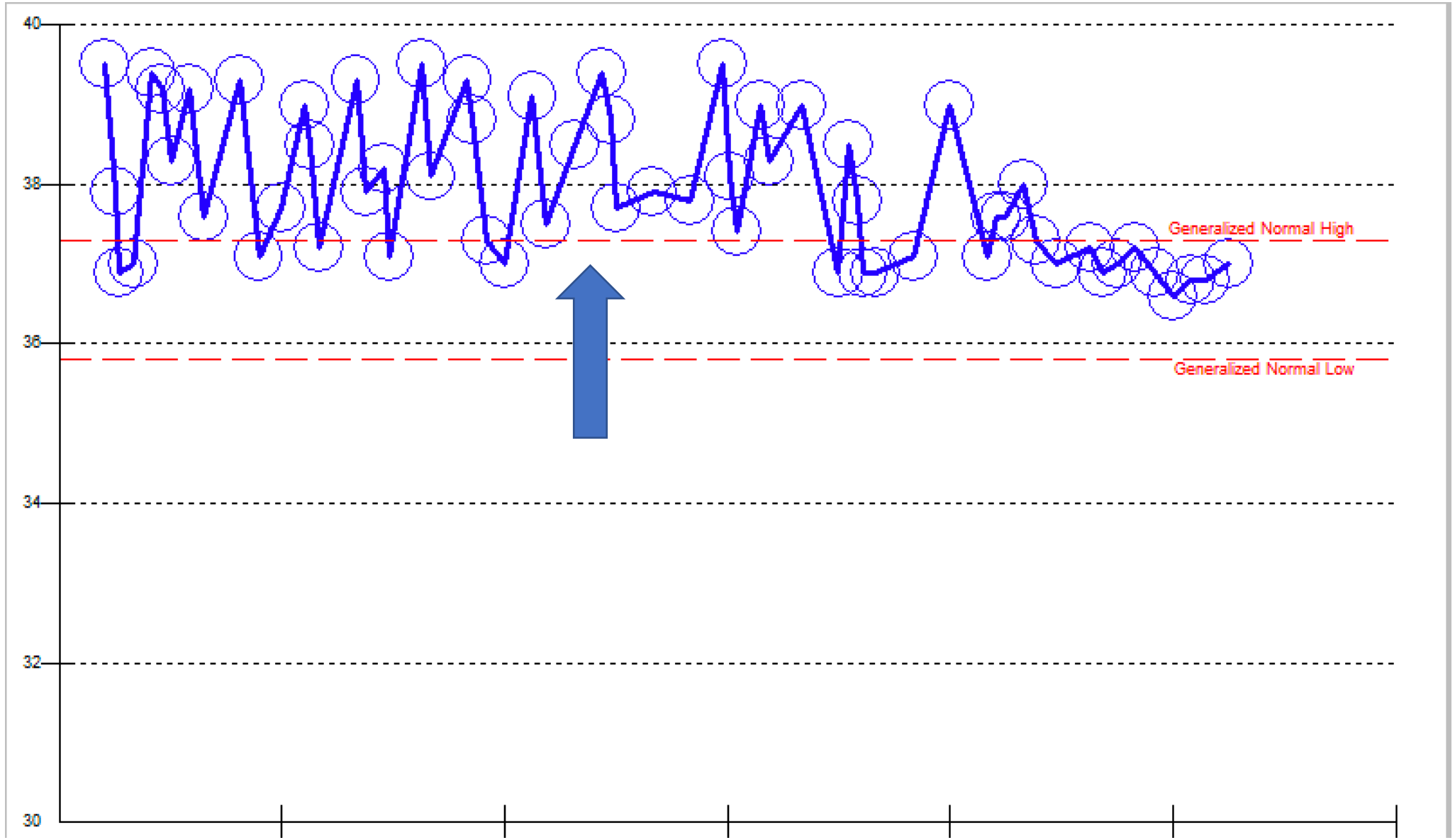
- Recommended Ceftriaxone and Flagyl initially
- Initial Blood Cultures: Salmonella Paratyphi A

	Salmonella species	
Drug	MIC Interp	MIC Dilutn
Ampicillin	S	<=8
Ceftazidime	S	<=1
Ceftriaxone	S	<=8
Ciprofloxacin	R (c)	Na (c)
Trimethoprim/Sulfa	S	<=2/38

- Flagyl stopped once speciation obtained, continued on Ceftriaxone

Hospital Course

- Defervesced ~ 4 days after initiation of antibiotics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Generalized Normal High
Generalized Normal Low

Hospital Course

- Defeversced ~ 4 days after initiation of antibiotics

- Labs on D'C
  - WBC 4.2 w/ ANC ~ 3500
  - PLT: 170
  - Transaminases normal

- D/C home on PO Cefpodoxime

Any specific preventive measures for patients traveling to areas with increasing incidences of S. paratyphi?

Preventive Measures

- Enteric Fever generally thought to be acquired d/t poor sanitation
  - Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. *JAMA 2004 Jun 2*
  - Retrospective review of 114 cases of Enteric Fever in Jakarta Indonesia
    - 26 (3%) of patients had Paratyphi A
  - Paratyphoid more commonly from community
    - Consumption of food from street vendors (OR 3.34 [CI] 1.41-7.91)
    - Flooding (OR 4.52 [CI] 1.90-10.73)
  - Typhoid acquired from home
    - Recent typhoid fever in household (OR 2.38 [CI] 1.41-7.91)
    - Sharing food from same plate (OR 1.93 [CI] 1.10-3.37)
    - No use of soap for handwashing (OR 1.91 [CI] 1.06-3.46)
    - Lack of toilet in household (OR 2.20 [CI] 1.06-4.55)

Preventive Measures

VACCINE	TYPE	ROUTE	DOSE AND INTERVAL	MINIMUM AGE (yr)	PROTECTION AGAINST *S.* TYPHI	BOOSTING INTERVAL IN TRAVELERS
Ty21a	Live attenuated	Oral	Four doses (in United States) Administer one dose every other day until complete	5*	50%-80%‡	Every 5 yr
Vi capsule antigen	Polysaccharide	Intramuscular	1	2	50%-80%	Every 2 yr

Limited immunity for children < age of 2

Lack of long-lasting immunity

Lack of protection against S. paratyphi A

Some evidence of protection against serotype B