

Case Presentation

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Sept 17, 2007

Hospital Course

July 14th

- Develops thrombocytopenia
- **Abx** changed to vancomycin, cefepime, and flagyl
- **HIDA scan:** Initial rapid hepatic parenchymal isotope uptake in fairly uniform distribution of isotope in mildly enlarged liver. No isotope accumulation within the gallbladder, consistent with acute or chronic cholecystitis

History of Present Illness

- Subject is a 36 y/o Caucasian female with a 15 year history of rheumatoid arthritis (RA).
- Disease initially involved feet and knees but subsequently involved the shoulder, elbows, wrists, and hands. Subject had bilateral forefoot surgery in 12/06 to correct deformities from RA.
- Treated with disease modifying anti-rheumatic drugs (DMARDs) since the early 1990s, including TNF inhibitors since 2002 when enrolled in open label clinical trial for etanercept (Enbrel). Trial lasted 3 mos. but TNF antagonists continued. Also treated with methotrexate and prednisone.
- Subject had persistently swollen and tender right knee for which received ten intra-articular steroid injections from 2000 to November 2006. She also received injections into left knee and R. subtalar. Six injections given between 2005 and 2006.

History of Present Illness

- **February 12, 2007:** Subject enrolls in the Phase I/II study for Intra-Articular Administration of tgAAC94 in Inflammatory Arthritis.
 - She met all inclusion criteria
 - Screening labs were within normal limits (WNL)
- **February 26th:** First injection of active study agent, tgAAC94
 - Dose= 5×10^{13} DNase resistance particles (DRP) into target joint (right knee).
 - Labs drawn that day were WNL (including a CBC, chemistries and liver function tests)
Synovial fluid drawn from right knee revealed no signs of infection.

History of Present Illness

■ Swelling of right knee

- Time of injection through Week 4: **Moderate**
- Week 4 (**March 28th**) study visit: **Mild**
- Week 8 (**April 23rd**) through **July 2nd**: **Moderate**

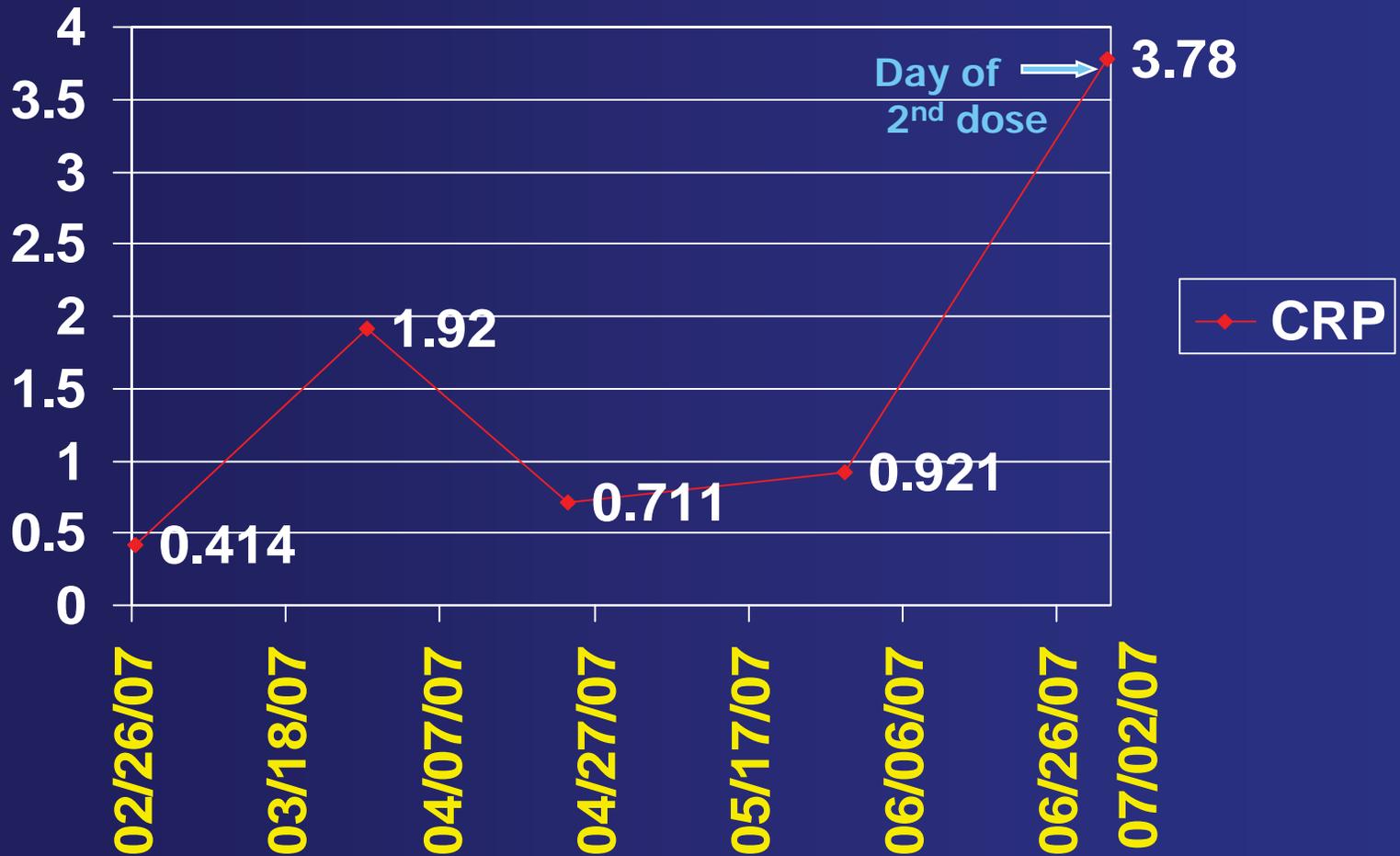
■ Pain

- Screening visit and at the time of the first injection: **Moderate**
- **March 6th** through Week 12 visit (**May 29th**): **Mild**
- Week 18 visit (**June 26th**): **Moderate**

History of Present Illness

- Blood counts, chemistries and liver function tests
 - WNL prior to the first dose, **Weeks 4, 8, 12,** and **July 2nd** (day of the second dose)
- AAV antibody titers increase to 1/128
- Increased C-reactive protein on day of second dose

C- Reactive Protein



History of Present Illness

- **June 22nd**: Contemporaneously with participation in clinical trial, subject's private physician prescribed by phone 5 days of valacyclovir for a presumed herpes infection.
- **June 28th**: Gynecologist prescribed by phone 7 days of metronidazole for infection. Subject reportedly did not take the full 7 day course.
- **June 29th-30th**: Subject reported increased fatigue.
- **July 1st**: Subject reported unusual fatigue and low grade fevers.

History of Present Illness

- **July 2nd:** Subject goes to work, and then to rheumatologist to receive second injection. She reported fatigue and low grade fevers (temperature of 99.6° F). Synovial fluid drawn that day revealed no infection.
- **Evening of July 2nd:** Nausea, vomiting, high fevers, chills. Subject subsequently experienced diarrhea and abdominal pain, mainly in the epigastric area.

History of Present Illness

- **July 3rd**: Fever to 101° F.
- **July 4th**: Vomiting and fever to 102° F, but reportedly felt better later in the day.
- **July 5th**: Visits PCP with c/o fevers for four days that ranged from 99° F to 102° F. Temperature 99° F. Physical exam unremarkable. Chest X-ray normal. Levofloxacin 500mg once a day prescribed.

History of Present Illness

- **July 6th**: Ill in morning but reportedly slight improvement in afternoon.
- **July 7th**: Seen in ER with Temp. 104 ° F
Reports nausea/vomiting and a headache.
 - **Chest x-ray** No active disease
 - **WBC 7.2**
 - **Hgb 12.8**
 - **Na 133**
 - **CO2 21.7**
 - **Creatinine 1.0**
 - **Blood and urine cultures** Neg.
 - **Dx**: Viral syndrome.
 - Promethazine for nausea

History of Present Illness

- **July 9th**: Sees Investigator and complains of intermittent fevers, headaches and vomiting.

Exam significant for:

- tachycardia (above 100)
- non-tender abdomen
- moderately swollen and tender right knee

Informs Investigator planning to f/u with PCP that day and that she is taking antibiotics.

History of Present Illness

- **July 9th**: Sees PCP complaining of “flu-like symptoms”, nausea and difficulty sleeping. Reports on ER visit and that promethazine stopped due to itching. PCP stops levofloxacin prescribes prochlorperazine.
- PCP draws labs (reported later) which show:
 - WBC 29,000 (Diff N²¹ B²¹ L⁵⁵)
 - AST 162
 - ALT 125
 - Bilirubin_T 1.2 Alk Phos 139
 - Additional serologies for acute hepatitis, CMV, parvovirus, mononucleosis, and Ehrlichia are negative.

History of Present Illness

- **July 11th**: Subject has abdominal distention and notes enlargement in area of liver
- **July 12th**: Admitted to local hospital with complaints of abdominal pain, nausea, vomiting, diarrhea, fever, chills. Appeared jaundiced. Temp. 103°F BP100/60

WBC: **17.6** (N³⁵ B²⁷ L³⁸) Hg/Hct **12/34** Platelets **86**

Chem: Na **134** Bicarb **20**, Cl **94** Glu **90**

BUN/Creat. **20/ 0.7** ALT **147** AST **291** Alk. P **455**

Bili_T **3.4** Alb. **2.9** Protein **5.6**

PmHx: RA diagnosed in 1992
Recurrent episodes of bronchitis
History of recurrent HSV infection

Surg Hx: Forefoot surgery 12/2006

Allergies: Aspirin (facial swelling)

Social Hx: Married with one young child. Working full-time in office setting. Rare alcohol consumption, no tobacco or illicit drugs. Recently boating on fresh water. No international travel. Subject grew up in Indiana.

Family Hx: non-contributory

DMARD History

1992 – 2000

- **Plaquenil** 1992(?) - 1994
- **Methotrexate** 1994-1999 (stopped due to anticipated pregnancy)
- **NSAIDS** early 1990's through 2007

1999 – 2001

- **Azathioprine (Imuran)** 125 mg per day
- **Prednisone** 7.5 mg

Fall 2001 – Summer 2002

- **Azathioprine** discontinued due to pregnancy (Fall 2001)
- **Prednisone** continued with doses as high as 20 mg/ day

Summer 2002 – Fall 2004

- **Methotrexate** restarted at 7.5 mg/week (Summer 2002)
- **Prednisone** titrated down
- **Etanercept (Enbrel)** started in Winter of 2002

2004

- **Adalimumab (Humira)** started Fall 2004 in lieu of entanercept after flare sxms in spring 2004

Current Medications

Etodolac 400 mg PO twice daily

Prednisone 2.5mg mg once a day

Methotrexate 20 mg subcutaneously once a week, 2004 - present

Adalimumab 40 mg subcutaneously every other week, 2004 - last dose 6/22/2007 (?)

Folic Acid 1 gram one per day

Orthonovum on PO once a day

Valacyclovir 500 mg twice daily, 6/22-27/2007

Metronidazole 500 mg twice daily, 6/28/2007 - 6/30/2007

Acetaminophen 500 mg, 2-4 tablets daily, during initial illness

Prochlorperazine 10 mg #20, started 7/9/2007

Hospital Course

July 12th - 13th

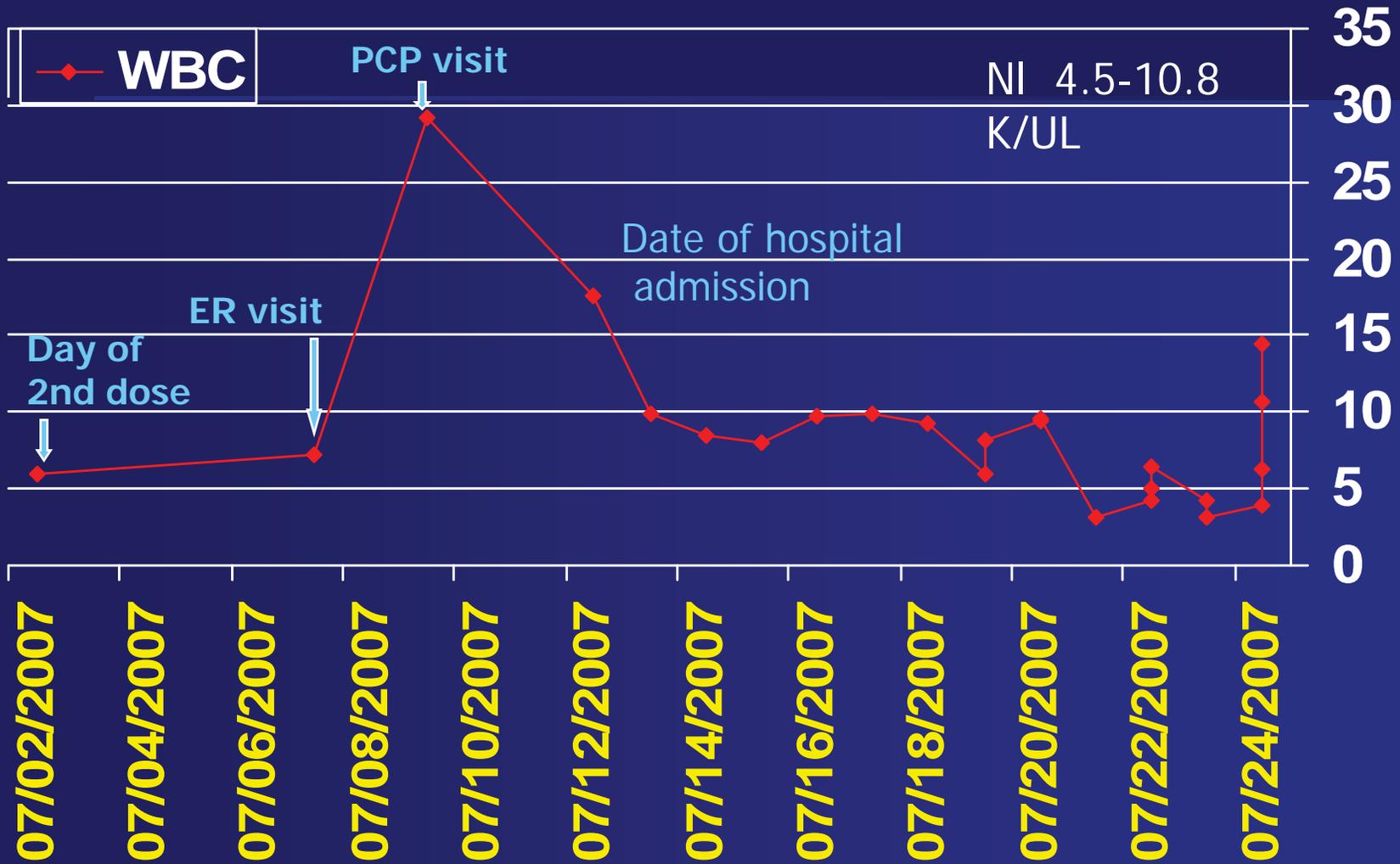
- Subject started on Meropenam and Levofloxacin
- **CAT scan:** Significant amount of pericholecystic fluid which may indicate cholecystitis but is non-specific. Moderate amount of free pelvic fluid.
- **Chest X-ray:** No Active Disease

Hospital Course

July 15th

- Subject remains febrile on antibiotics. WBC is down but smear continues to show: vacuolated neutrophils, toxic granulation, Dohle bodies and reactive lymphs
- **Ultrasound Gallbladder** Mild splenomegaly. No significant focal intra hepatic lesions demonstrated. Partially contracted gall bladder with mild diffuse gallbladder thickening. No definite evidence of cholelithiasis nor biliary duct dilatation. No evidence of pericholecystic fluid nor abscess.

White Blood Cell Counts



Hospital Course

July 16th-17th

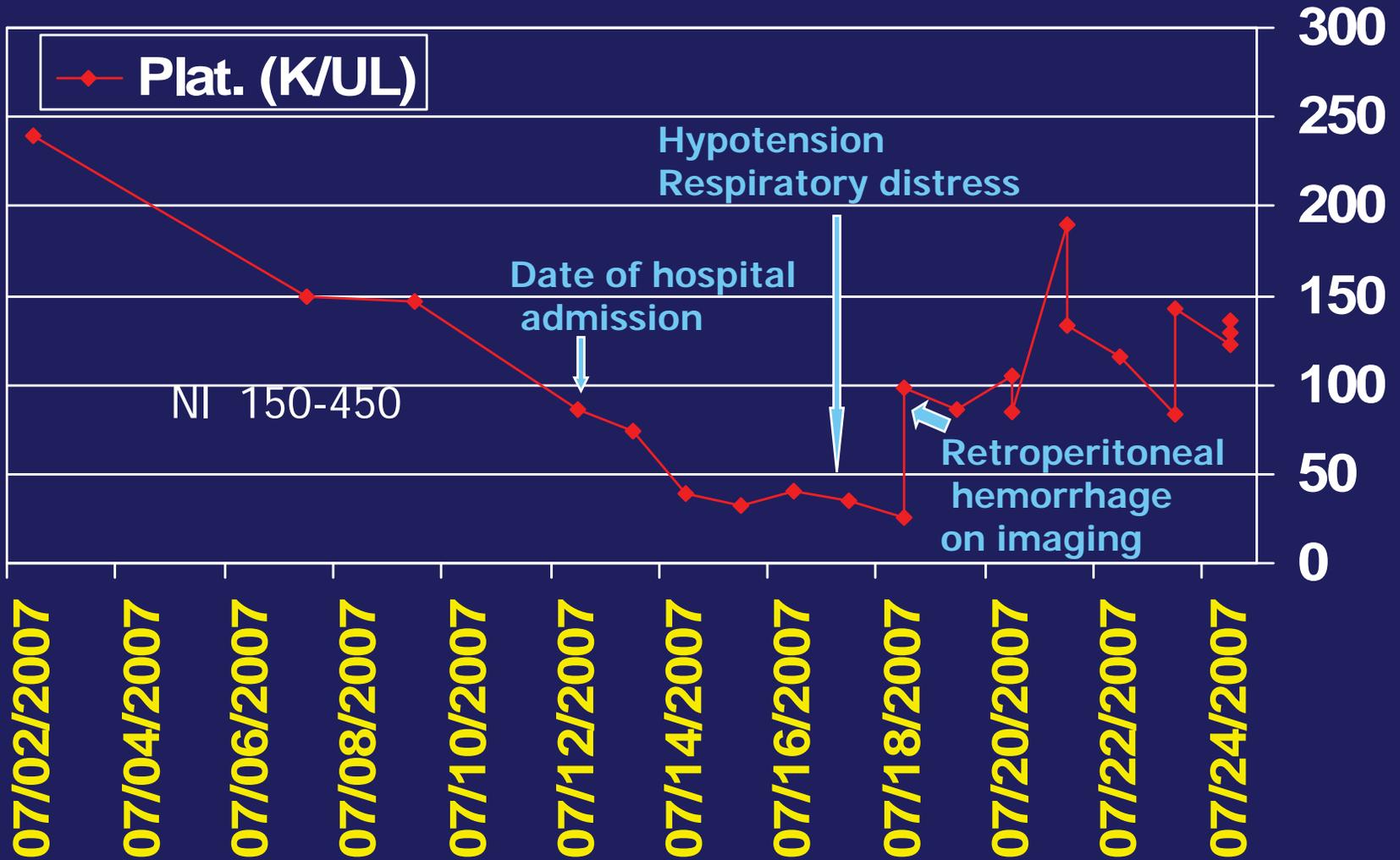
- Hemoglobin begins to drop, coagulation tests abnormal, liver function tests continue to rise.
- Blood transfusion given.
- Episode of hypotension (Systolic to 60s) and respiratory distress requiring intubation and ionotropes.
- ABG: 7.368 pCO₂ 17.9 pO₂ 99.3 0.5 L
- Acute drop in Hemoglobin to 4.6.
- Develops acute renal failure, UA with 318 RBCs.

Hospital Course

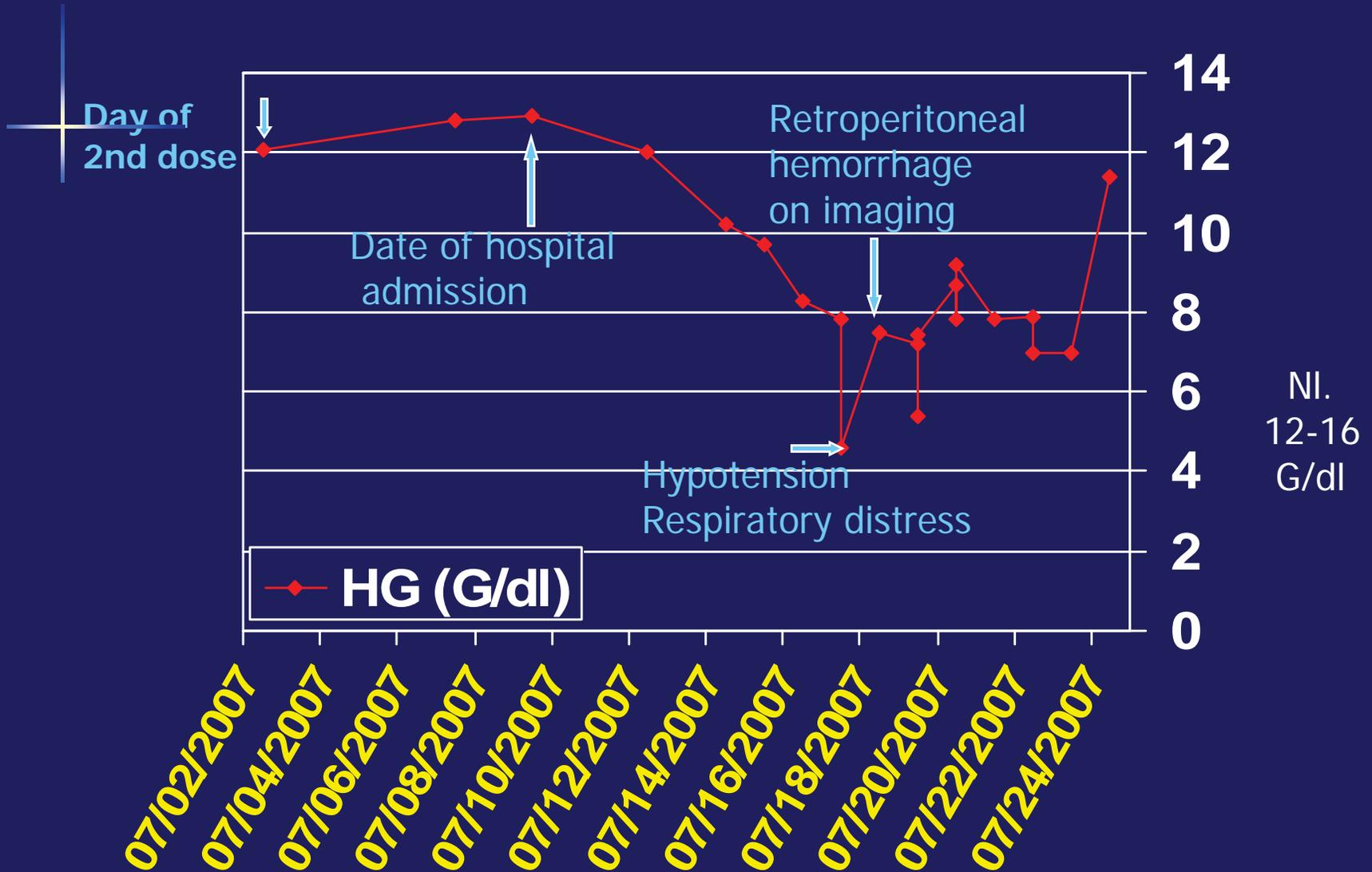
July 18th

- Intubated but awake, oliguric, febrile.
- **Multiple transfusions:** 10 units PRBCs, 6 Fresh Frozen Plasma, 6 Cryoprecipitate, IV fluids over past 48 hours.
- **Ultrasound Abdomen:** There is hepatopetal flow in the portal vein without portal vein thrombosis. Posterior to the left kidney is a 8.6 cm diameter cystic structure demonstrating septations heterogeneity of both cystic and solid components. Has ultrasound appearance of **organizing hematoma or hemorrhage in the left retroperitoneal space.**
- Subject transferred to University of Chicago.

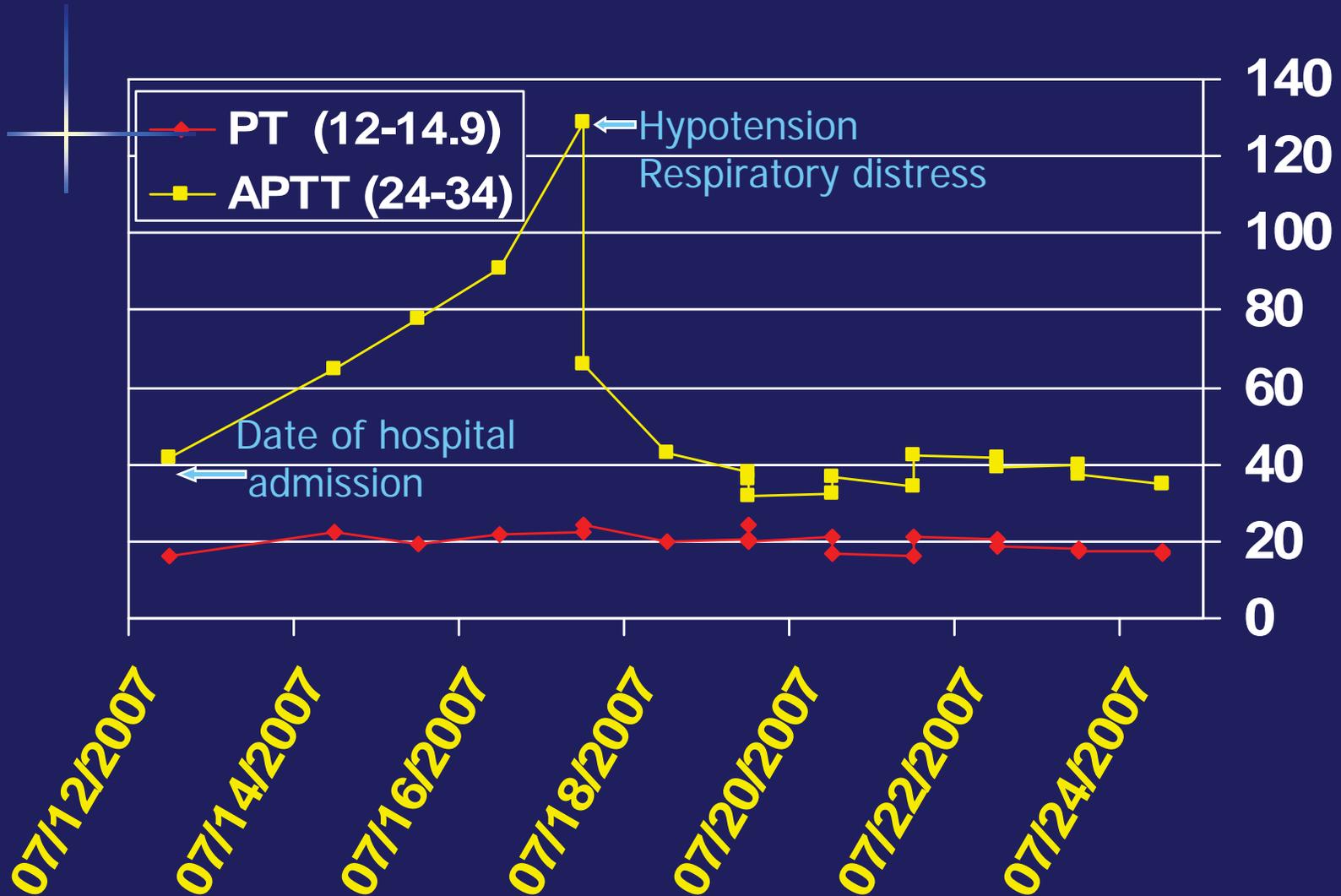
Platelets



Hemoglobin Levels



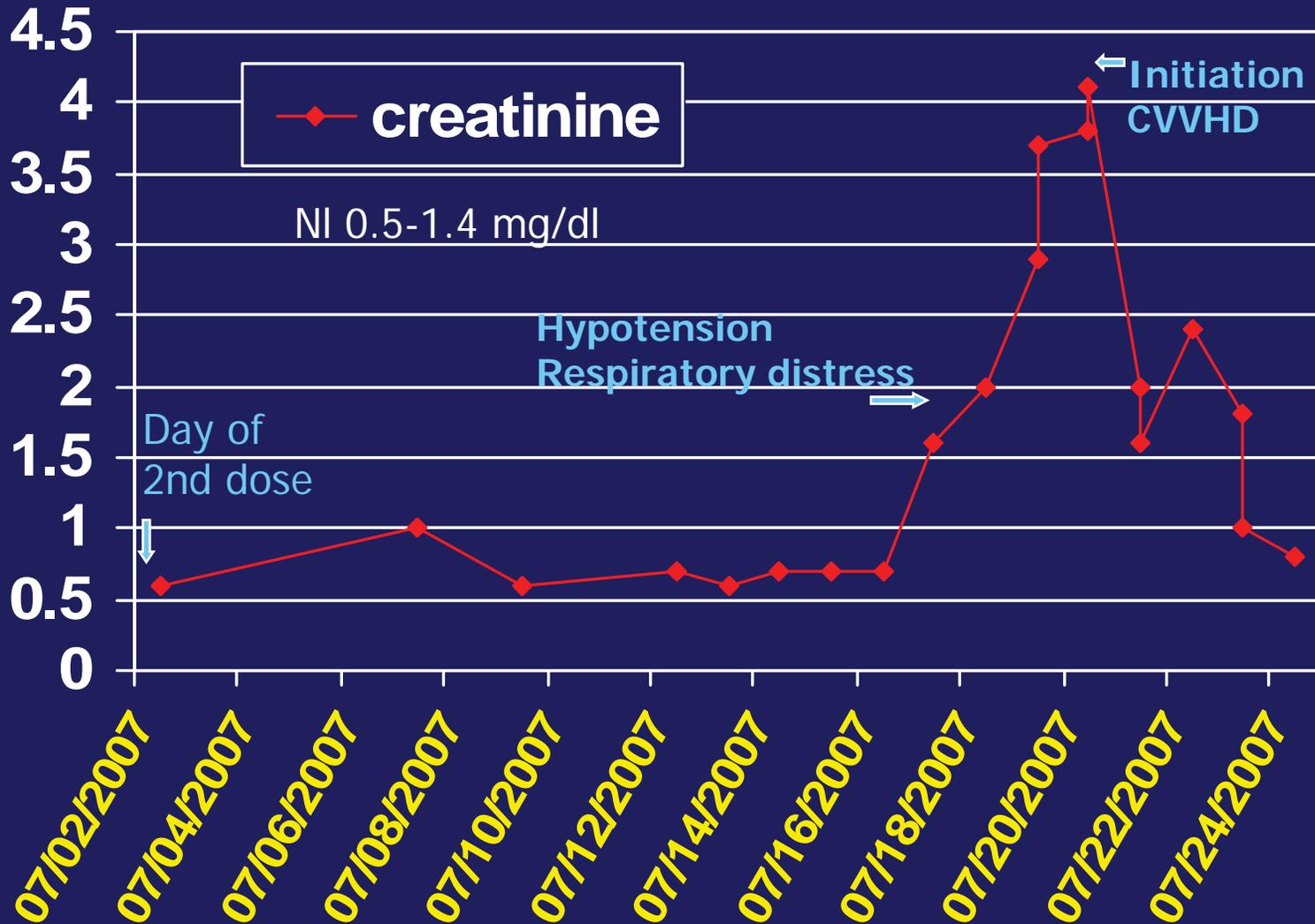
Coagulation



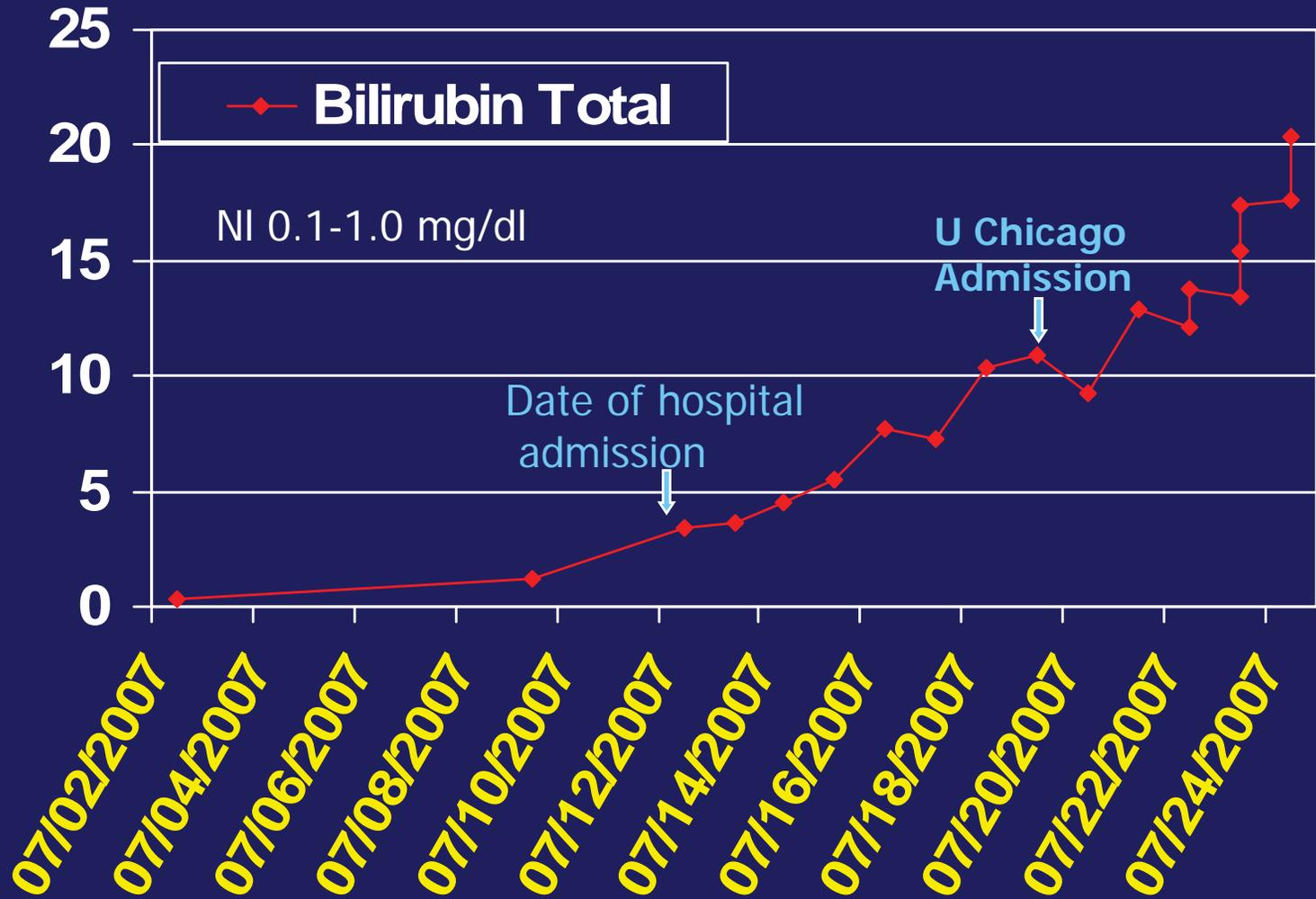
Hematologic Labs

<p>Fibrinogen (180-409 mg/dl)</p> <p>7/14 101</p> <p>7/17 86</p> <p>7/18 160</p>	<p>Fibrogen Split Products (<10)</p> <p>7/14 80</p> <p>Thrombin Time (8-14 sec)</p> <p>7/16 10</p>		
<p>D- Dimer (< 0.42 UG/ml)</p> <p>7/20 15.1</p> <p>7/22 >20</p>	<p>HIT antibody (<0.400)</p> <p>7/20 0.456</p>		
<p>Factor V (75-137%)</p>	<p>7/16</p> <p>60*</p>	<p>7/20</p> <p>109</p>	<p>7/22</p> <p>72</p>
<p>Factor VII (71-147%)</p>		<p>89</p>	<p>73</p>
<p>Factor VIII (57-152%)</p>		<p>329</p>	<p>473</p>
<p>* Reference range for this lab (50-160%)</p>			

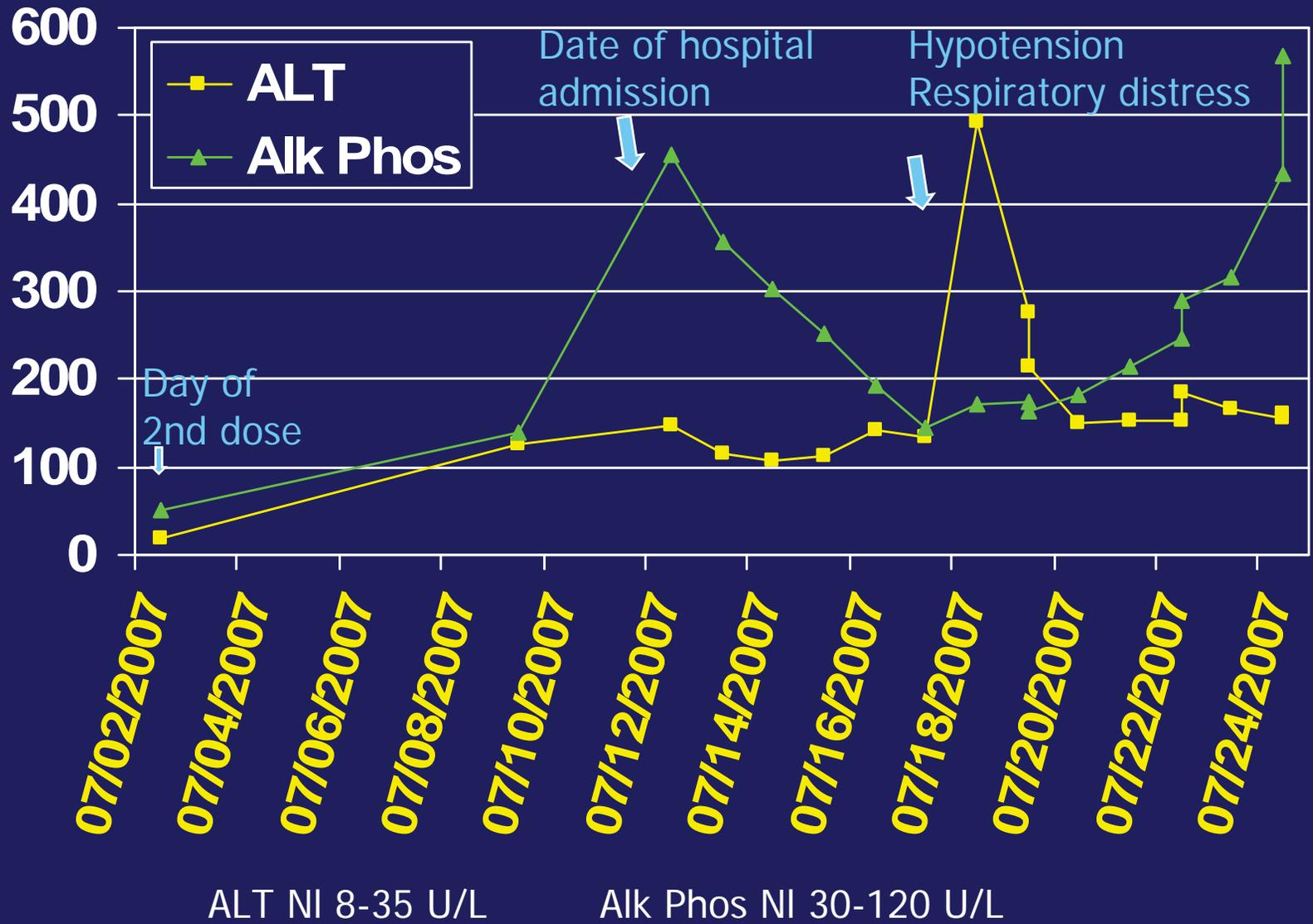
Kidney Test



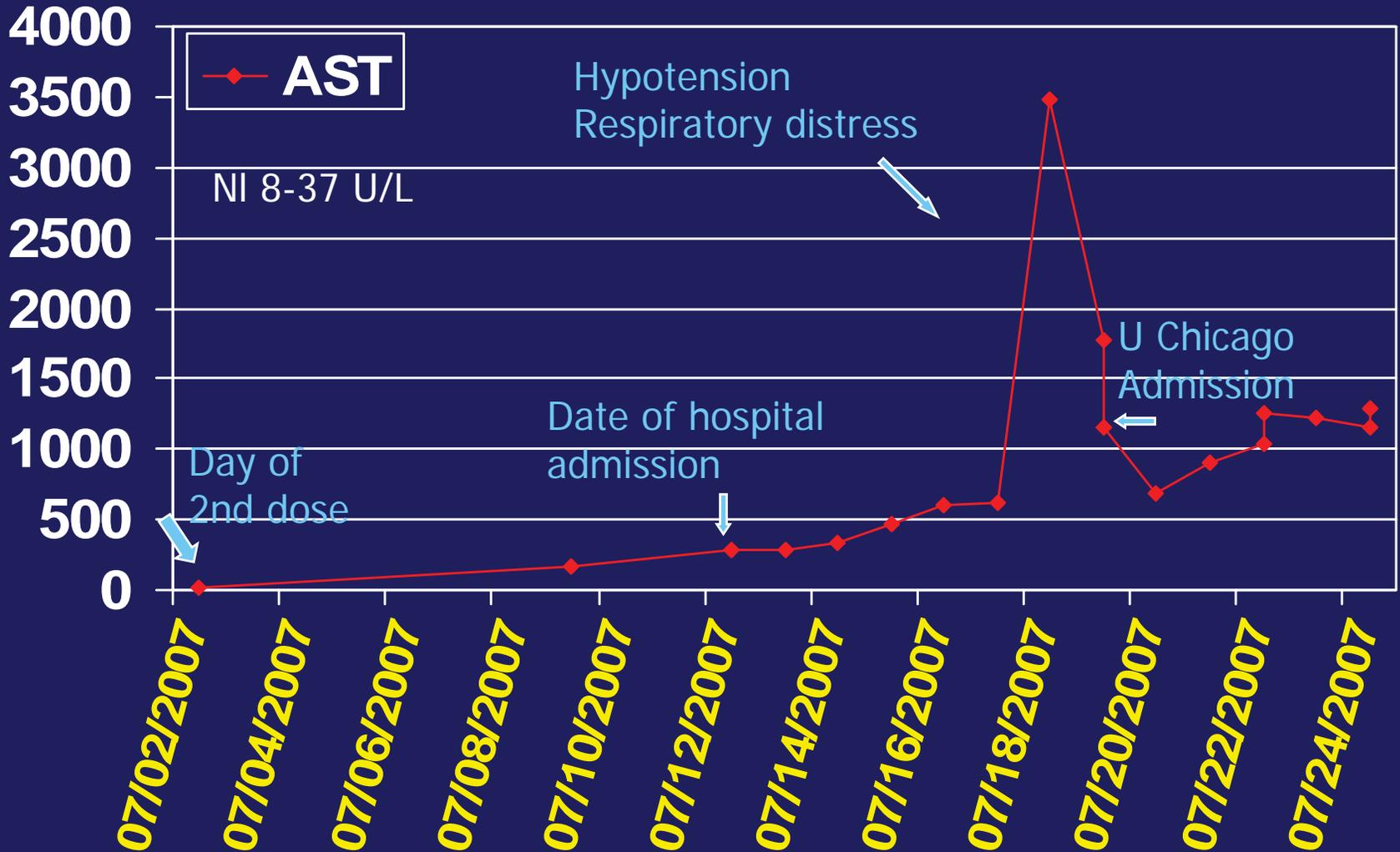
Liver Tests



Liver Tests



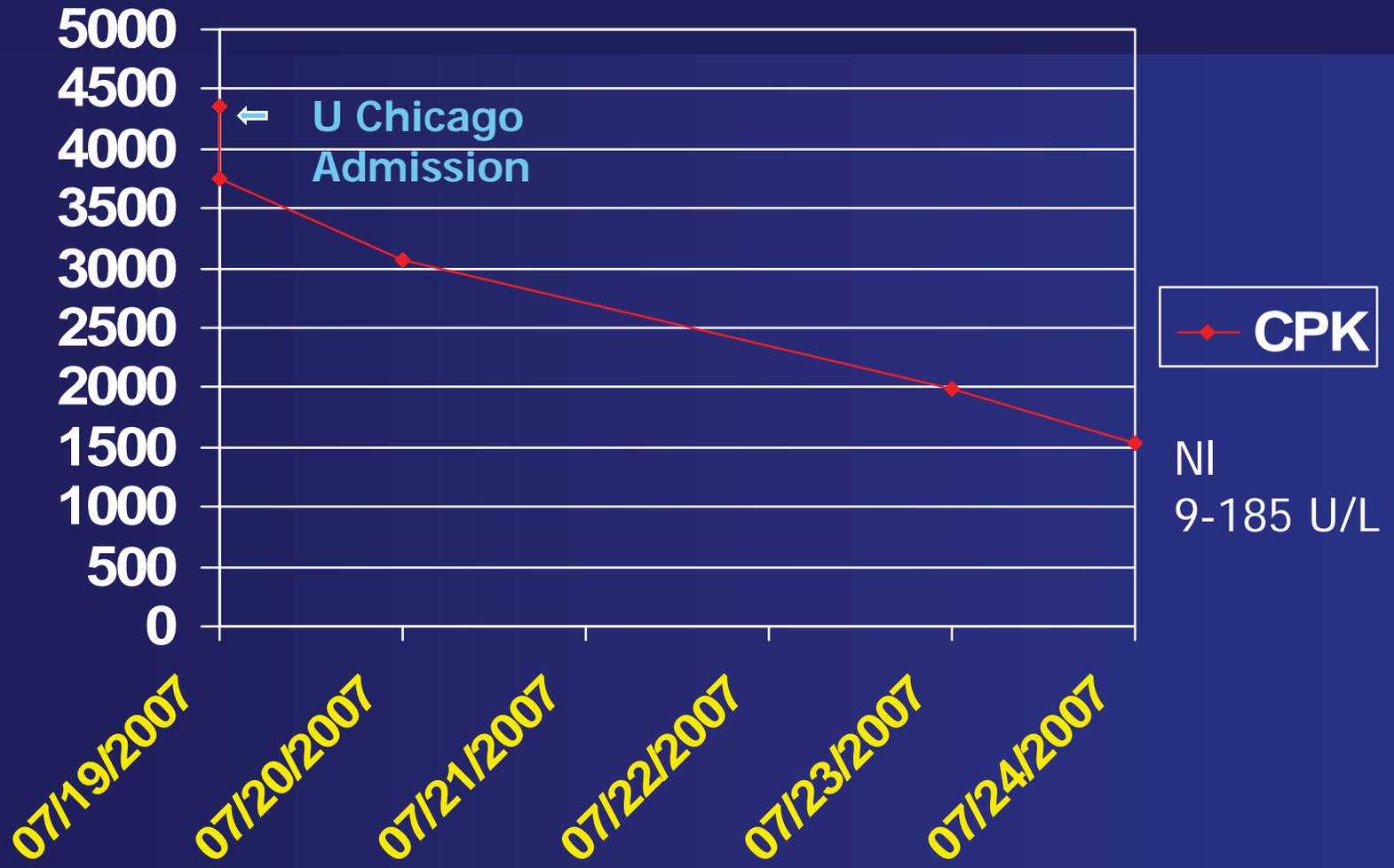
Liver Tests



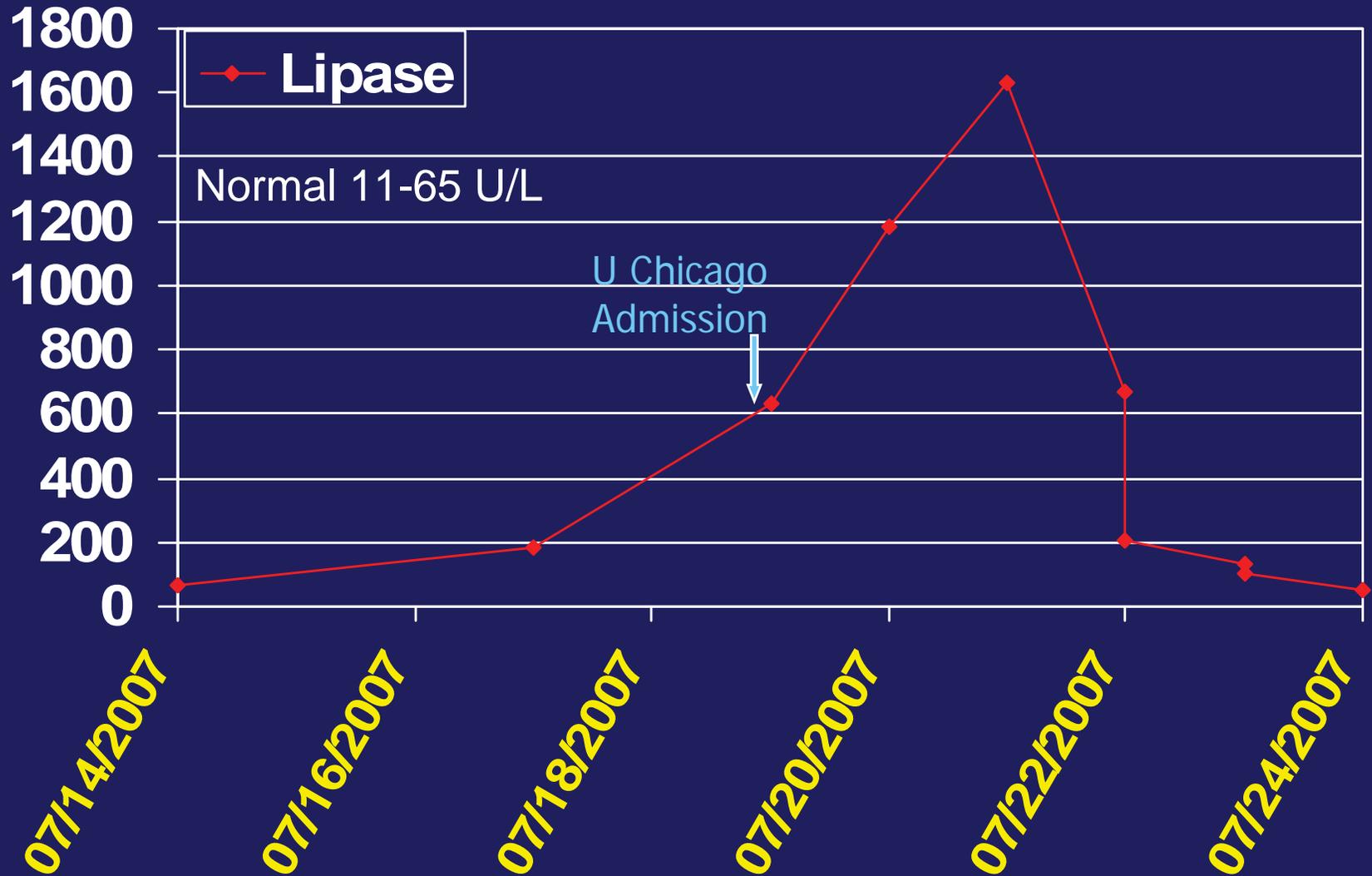
Serology and other Labs

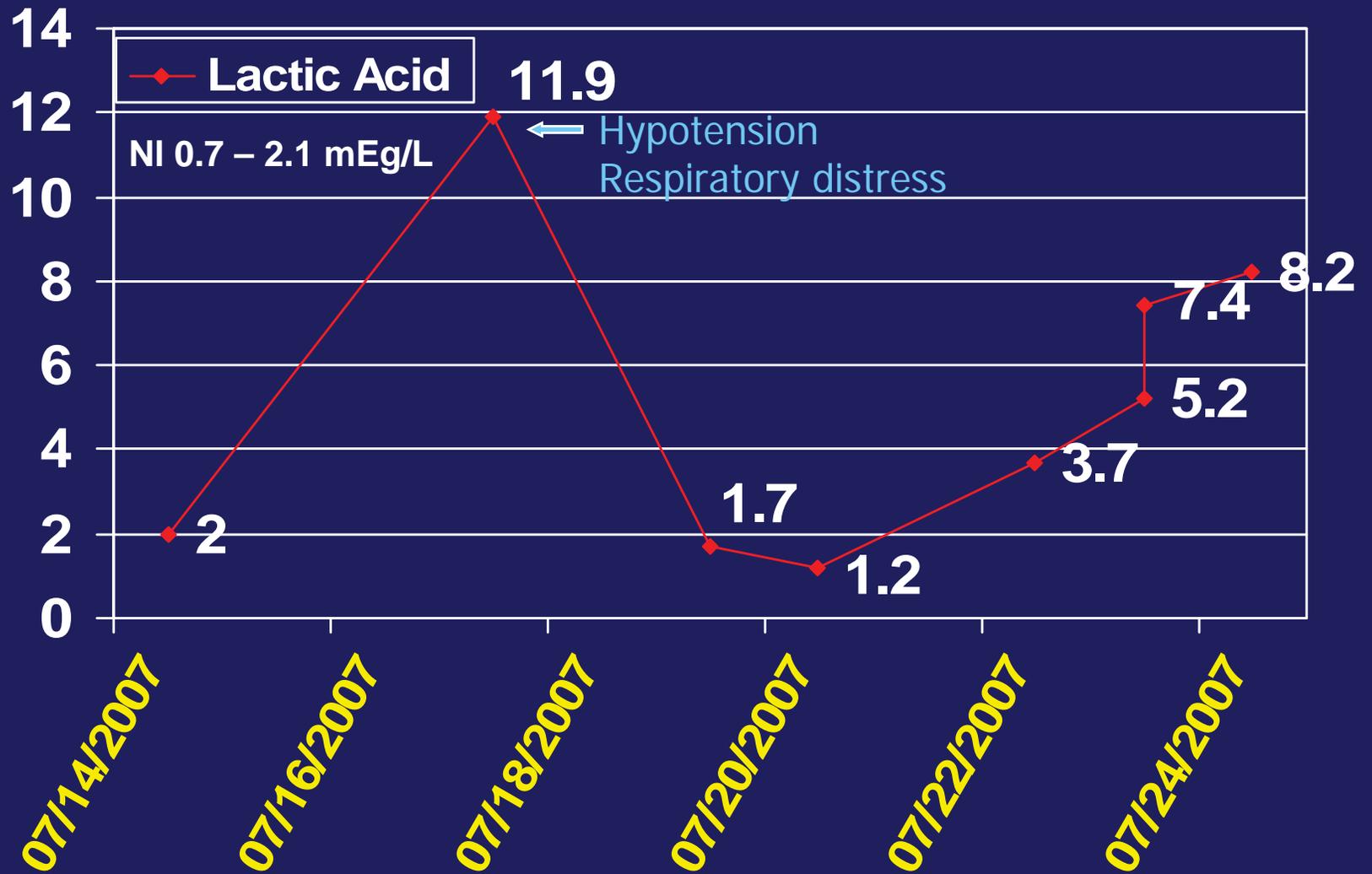
<p>IgA 160 IgG 694* (800-1700) IgM 89 CMV IgG pos IgM neg</p>	<p>HSV IgG Type 1 pos. Type 2 neg. HSV (I & II) qPCR300 copies/ml VZV q PCR Negative (Viracor)(7/18)</p>
<p>HepA IgM neg HepB core IgM neg Hep B surf Ag neg HepC ab neg</p>	<p>EBV capsid IgG 1:640 (<10) EBV IgM neg. EBNA +</p>
<p>ANA 160 (nl 0-80] Speckled pattern Smooth muscle antibody <25 DNA native Dbl strand <10</p>	<p>HIV1/HIV2 Ab EIA nonreactive Adenovirus qPCR Neg. (Viracor)(7/18)</p>

Creatine Phosphokinase (muscle)



Pancreas





Arrives at Univ Chicago

- Intubated and Sedated with P/P 50/20, down to 30/20 with ETT reposition.
- Lungs with decreased BS on left, ETT pulled back 2cm and clear BS bilaterally
- RRR s1/s2, no m/r/g. Prominent PMI
- Abd tender to palp. No fluid wave. No HSM noted. Bladder pressure is 22.
- Skin: no bruising. Jaundiced. Scleral icterus
- Ext: no erythema or swelling at knees

Arrives at Univ Chicago

- Abdominal pressures (as measured by bladder pressure) are elevated
- CVP is low
- MVO₂ is low
- Plateau pressures are high
- Urine output is diminished

Initial CXR

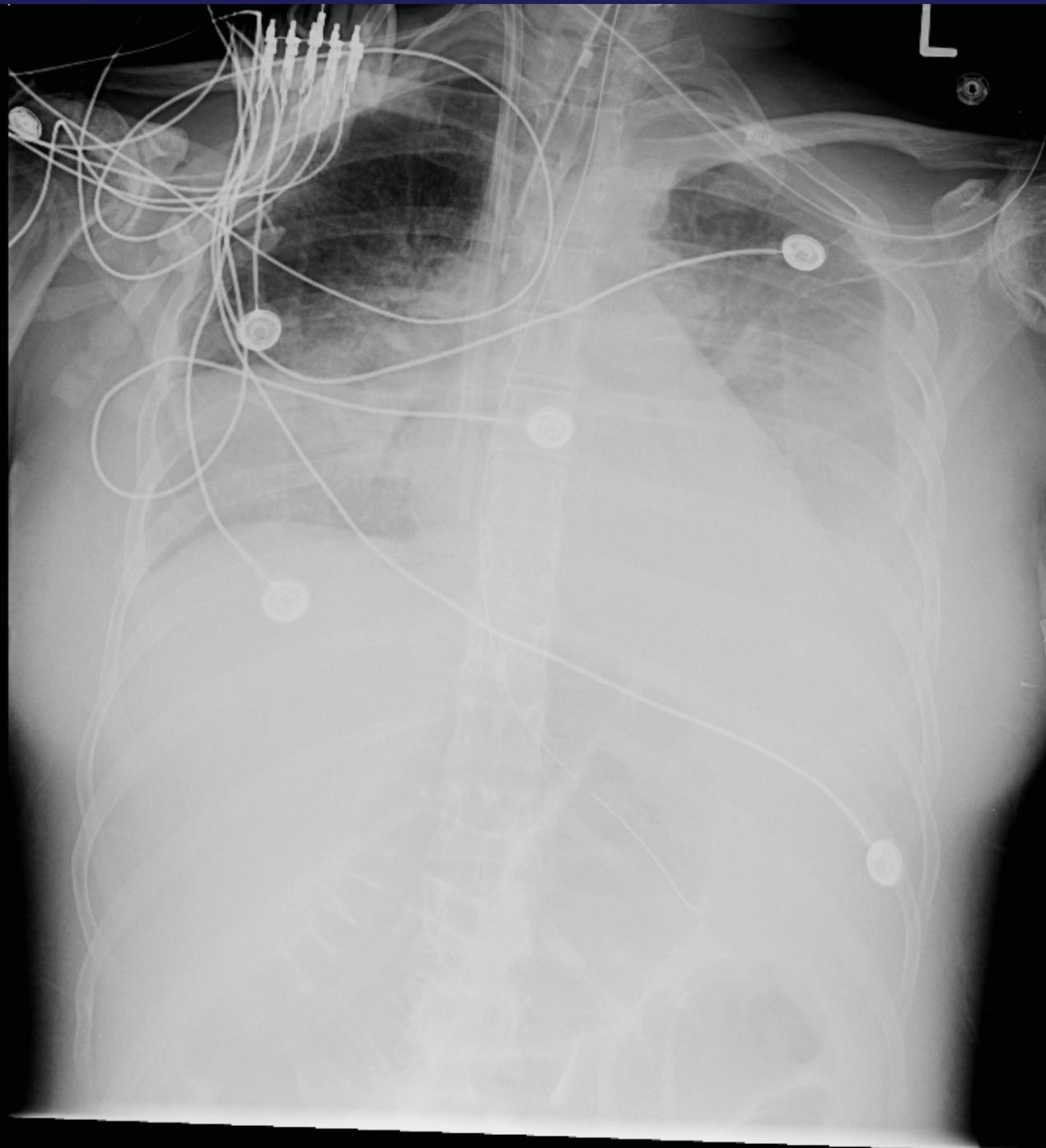


Image size: 512 x 512
View size: 1545 x 842
WL: 70 WW: 450

A

5/25/71 - 36 y
2960386
CT NON-INFUSED CHEST
AXL W-O
22790
3
NEW CHEST/ABD/PELVIS/Abdomen



R



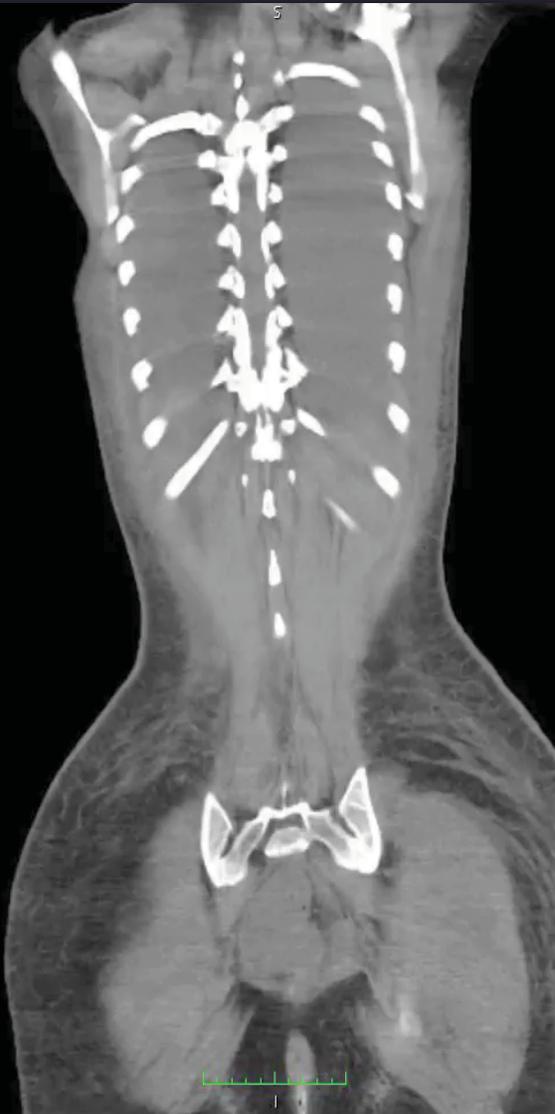
Im: 75/226
Zoom: 164% Angle: 0
Thickness: 3.00 mm Location: -131.40 mm



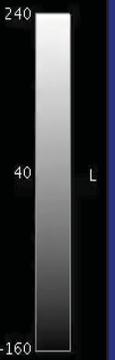
1:24:02 PM
7/19/07
Made In OsiriX

Image size: 512 x 512
View size: 1545 x 842
WL: 40 WW: 400

5/25/71 -36 y
2960386
CT NON-INFUSED CHEST
MPR, W-O, Coronal
22790
8028
NEW CHEST/ABD/PELVIS/ Abdomen



R



Im: 48/133
Zoom: 164% Angle: 0
Thickness: 4.00 mm Location: 216.96 mm

1:24:02 PM
7/19/07
Made In Osirix

Plan

- Liver: serologies, liver biopsy
- Renal: renal replacement therapy
- Heme: fix INR prn, maintain Hgb, r/o DIC
- Pulm: vent support
- CV: Keep CVP >10 and $MVO_2 >70\%$
- Endo: r/o adrenal insufficiency

Empiric Therapy

- Imipenem, Daptomycin, Micafungin
- Cultures sent. Micafungin was started b/c of yeast seen on a blood smear, but all cultures were negative to date
- Heme consult for ? Of TTP, DIC or Hemo-Phagocytic syndrome.
- Liver consult
- ID consult
- Renal consult

Clinical Course

- Unable to stop the retroperitoneal bleed despite massive transfusion of products and heme w/u negative for an intrinsic bleeding cause. Attempt at arterial embolization was unsuccessful at finding a source.
- CVVH initiated
- Liver injury improving
- Bladder pressures start to climb

Repeat Imaging

Image size: 512 x 512
View size: 1545 x 842
WL: 70 WW: 400

5/25/71 -36 y
2960386
CT INFUSED UPPER ABDOMEN
MPR, W-, Coronal
22890
80280
ABDOMEN PELVIS MED/Abdomen



R



Im: 41/126
Zoom: 164% Angle: 0
Thickness: 4.00 mm Location: 211.57 mm

5:31:22 PM
7/22/07
Made in Osirix

Image size: 512 x 512
View size: 1545 x 842
WL: 70 WW: 450

A

5/25/71 -36 y
2960386
CT INFUSED UPPER ABDOMEN
AXL W-
22890
3
ABDOMEN PELVIS MED/Abdomen



R

295
70
-155
L

Im: 20/182
Zoom: 164% Angle: 0
Thickness: 4.00 mm Location: 1042.70 mm

P

5:31:22 PM
7/22/07
Made In OsiriX

- Larger Hematoma
- Hypoperfusion of Spleen
- Hypoperfusion of Kidney

Clinical Course Continued

- Bladder pressures rising
- Plateau pressures rising on ventilator
- MAPs start dropping
- Continued need for pRBCs despite adequate INR and Plt.
- Pressor support started
- Increased Oxygen needed as CXR worsens with ARDS picture. Paralytic started
- Empiric dexamethasone started and stim test ordered

7/23

- Worsening oxygenation despite full oxygen, high PEEP, and paralytics.
- Code status changed to DNR
- Random Cortisol is 16, stims to 22.

7/24

- Worsening clinical status
- Goals changed to comfort care
 - BIS started to titrate sedation deeper
 - Paralytic lifted
 - Pressors stopped
 - Ventilator removed
- Patient dies 20 minutes after removing support.
- Blood cultures drawn on 7/24 turn positive 2 days post-mortem: *Histoplasmosis capsulatum* growing.