



84 years old female presenting with fever and altered mental status

Shadi Hassan
The Lady Davis, Carmel Medical Center
Haifa, Israel

ESIM, Saas-Fee, Switzerland
1.2011



History

- 84 years old, female
- One day of:
 - Fever $>38^{\circ}\text{C}$
 - Confusion
 - Tremor
 - Several vomiting



History

- s/p CABG – 1992
- s/p NSTEMI + Pulmonary Edema – 2007
- Congestive Heart Failure
 - Good LV Function + Diastolic Dysfunction II
- Hypertension
- Dyslipidemia
- Diabetes Mellitus
- COPD
- s/p Heavy Smoker
- Anemia – Normocytic
- s/p Cholecystectomy (due to cholelithiasis)



Physical Examination

- Temp. – 38.5°C
- 22 breaths/min, 98% O₂ saturation
- BP-211/88, HR-98
- ECG – NSR, 93/min, Q waves in III and AVF, no change from a previous ECG

- Confused, altered mental status
- Normal neurological examination
- Increased bowel movement sounds
- Mild diffuse abdominal tenderness



Laboratory

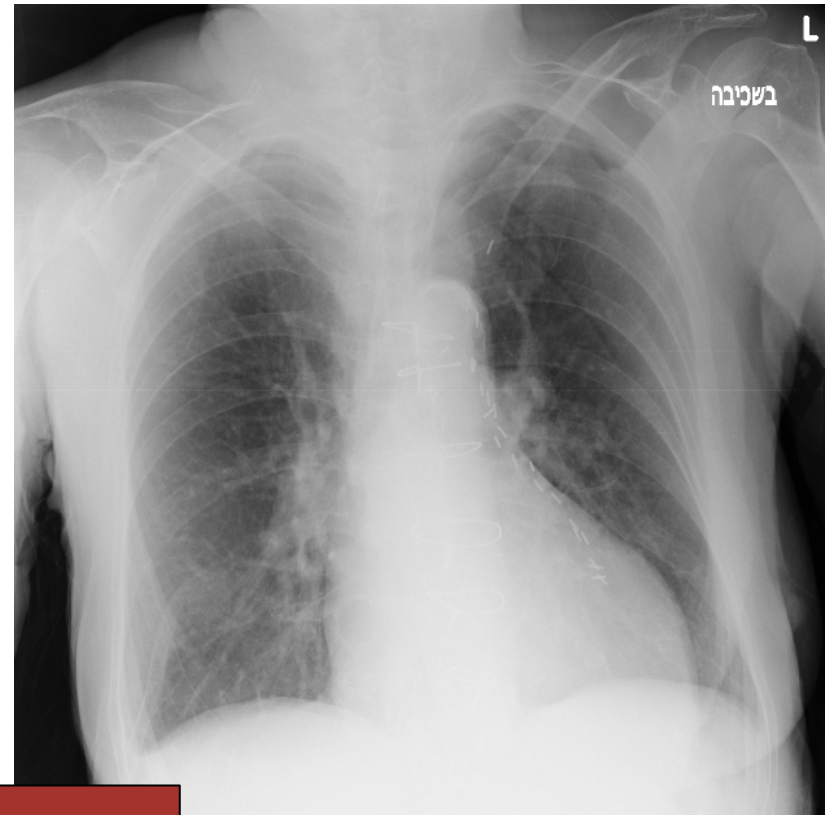
- Glucose- Normal
- Na – 135 mEq/L (135-145)
- K – 3.2 mEq/L (3.5-5.1)
- Other electrolytes - Normal
- CK, Troponin - Normal
- Renal, Liver, Pancreas – Normal



Laboratory

- WBC – **12,4** k/ μ L (4.8-10.8) , left shift
- Hb, PLT – normal
- CRP - normal
- PT,PTT – normal
- No signs of urine infection

Imaging



Normal

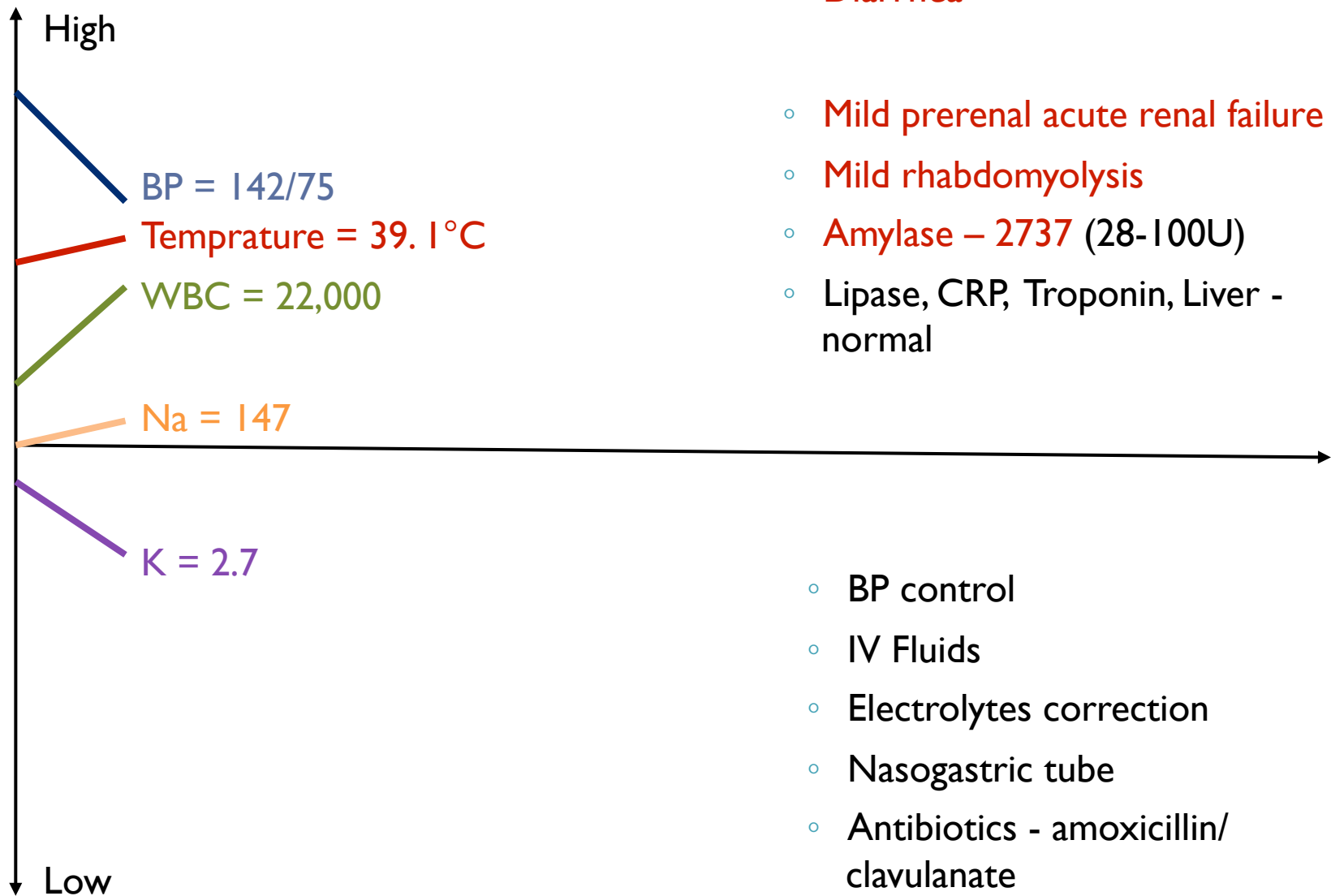




What would you do?

- Blood pressure control
- Neurological consult
 - Normal neurological examination
 - Lumbar puncture - normal
- IV Fluids
- Correction of hypokalemia
- Antibiotics
 - Sepsis? Aspiration pneumonia caused by vomiting?
 - amoxicillin/clavulanate

Day 2

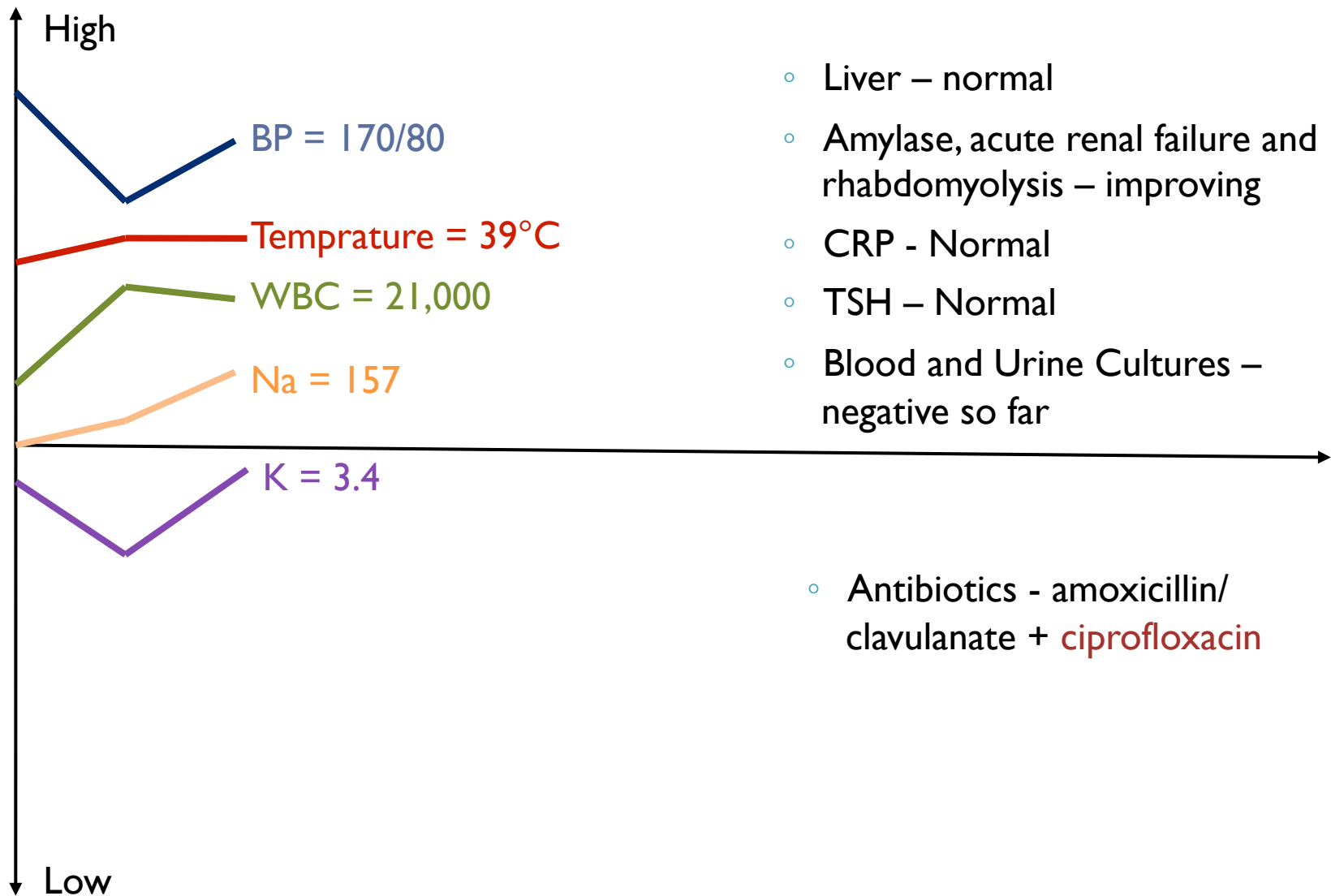


- Vomiting
- Confusion - worse
- Sweating
- Diarrhea

- Mild prerenal acute renal failure
- Mild rhabdomyolysis
- Amylase – 2737 (28-100U)
- Lipase, CRP, Troponin, Liver - normal

- BP control
- IV Fluids
- Electrolytes correction
- Nasogastric tube
- Antibiotics - amoxicillin/ clavulanate

Day 3



- Liver – normal
 - Amylase, acute renal failure and rhabdomyolysis – improving
 - CRP - Normal
 - TSH – Normal
 - Blood and Urine Cultures – negative so far
-
- Antibiotics - amoxicillin/
clavulanate + ciprofloxacin

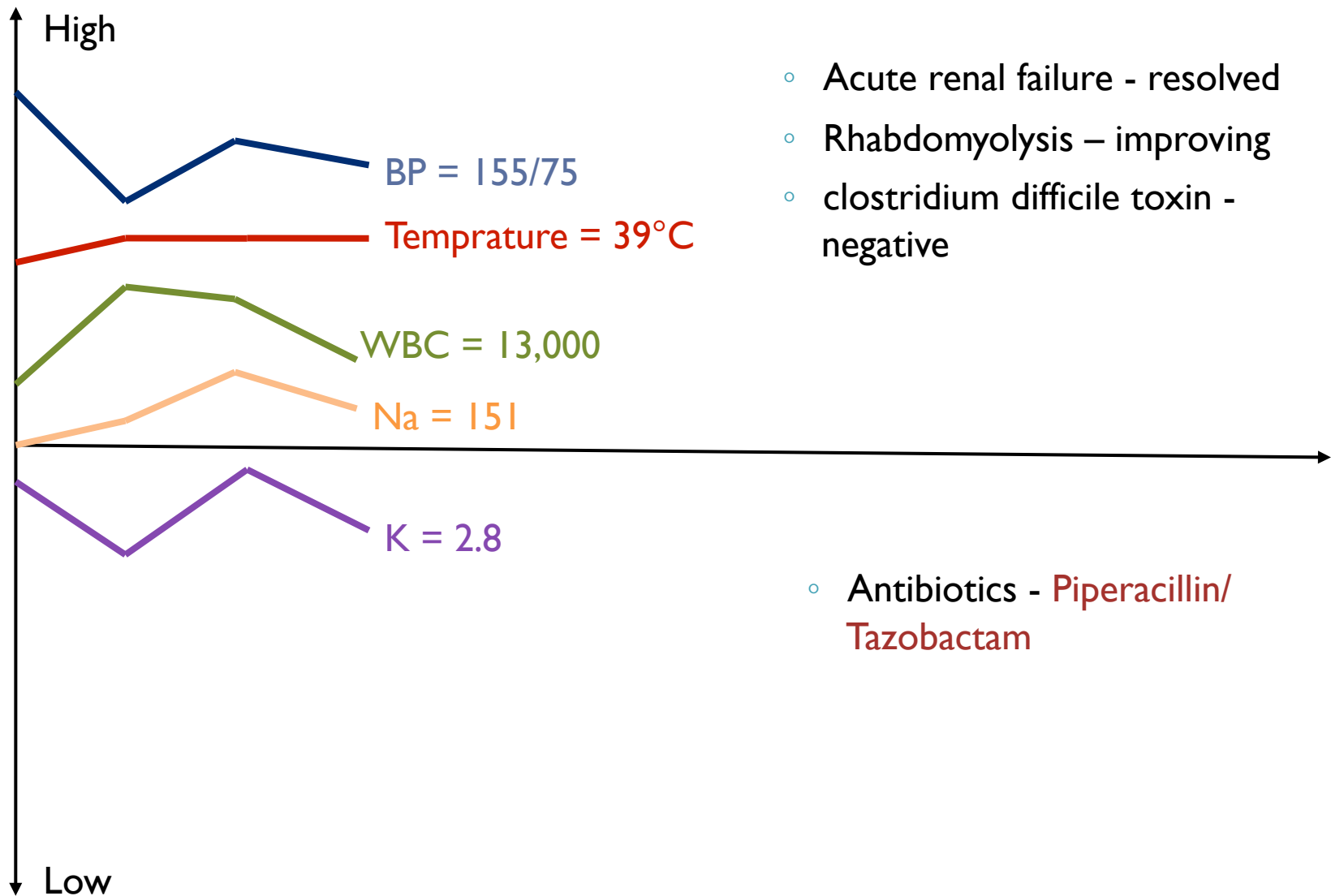
Day 4 – chest, abdomen and pelvic CTA



Normal



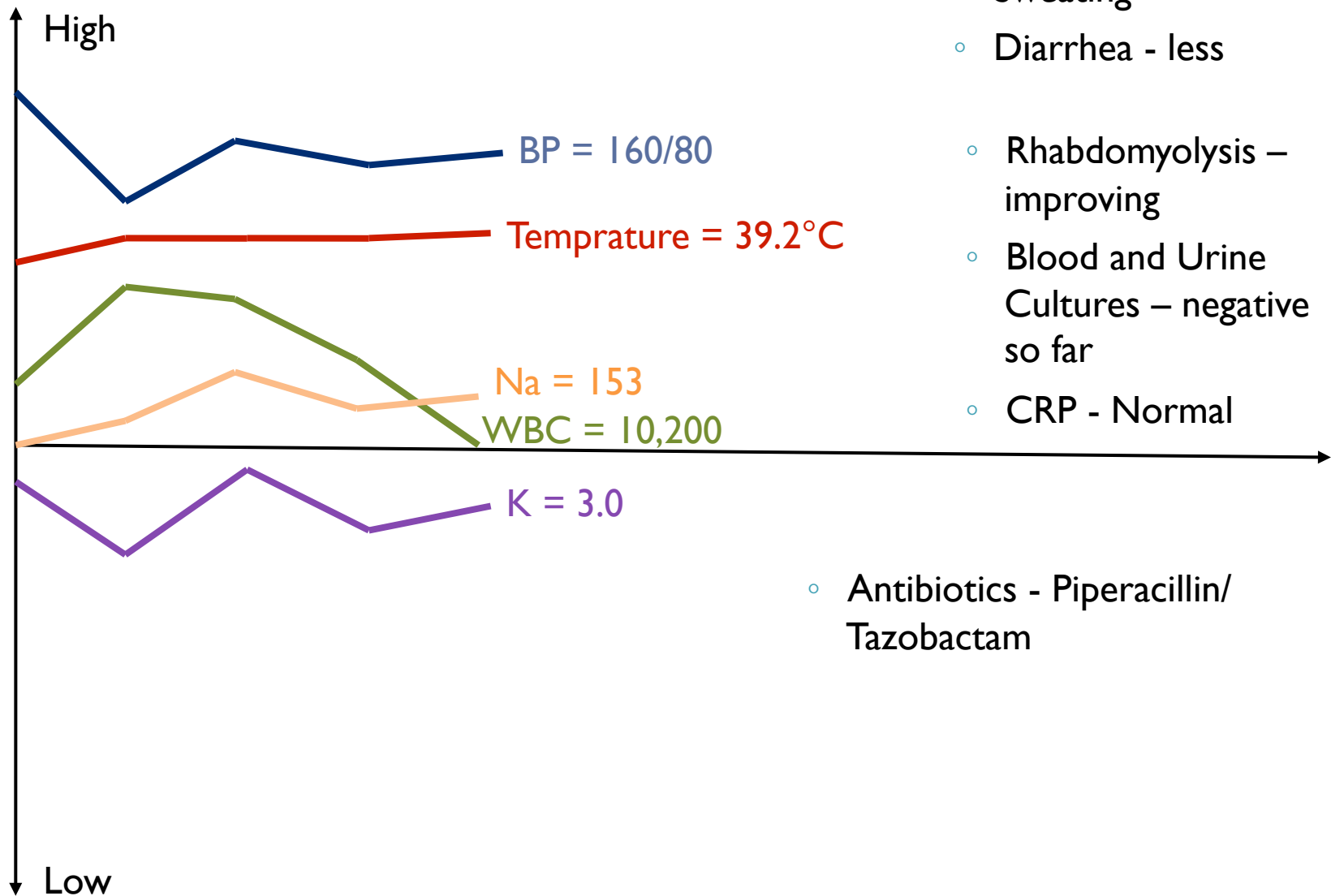
Day 4



- Acute renal failure - resolved
- Rhabdomyolysis – improving
- clostridium difficile toxin - negative

- Antibiotics - Piperacillin/
Tazobactam

Day 5



- No vomiting
- Nasogastric feeding
- Confusion
- Sweating
- Diarrhea - less

- Rhabdomyolysis – improving
- Blood and Urine Cultures – negative so far
- CRP - Normal

- Antibiotics - Piperacillin/Tazobactam



Why isn't our patient getting better?

- She was treated with Haloperidol for the last 3 months.
- Could it be- **Neuroleptic Malignant Syndrome?**



NMS

- Is a **life threatening** neurologic emergency
- associated with the use of **neuroleptic agents** and antiemetics
- 0.02-3% among patients taking neuroleptic agents
- **Mortality – 10-20%**
- Requiring a high clinical suspicion for diagnosis and treatment, NMS is appropriately **a syndrome more often considered than truly diagnosed.**



NMS – clinical features

- Characterized by a distinctive clinical syndrome of
 - **Mental status change**
 - the initial symptom in 82%
 - **Muscular rigidity**, tremor
 - **Fever**
 - **Dysautonomia**
 - Tachycardia, labile or high blood pressure , tachypnea, dysrhythmias, diaphoresis.
 - Each feature is present in **97-100%** of patients

NMS – associated medications

- **Antipsychotic medications**
 - "Neuroleptic" / "Typical"
 - "Atypical antipsychotic" or "second-generation antipsychotic"
- **NMS** - most often - "typical" high potency neuroleptic agents (eg, haloperidol, fluphenazine).
 - **symptoms** usually develop during the first two weeks
 - **Idiosyncratic**
 - after a single dose / treatment for many years
 - recent or rapid dose escalation, a switch from one agent to another, and parenteral administration as **risk factors**



NMS – Diagnostic Testing

- There is no diagnostic test for NMS
- Elevated serum CK
 - Usually CK > 1000
- Leukocytosis
 - 10,000-40,000
- LDH, alkaline phosphatase, and liver transaminases
 - Mild elevations are common.
- Electrolyte abnormalities
 - hypocalcemia, hypomagnesemia, hypo and hypernatremia, hyperkalemia, and metabolic acidosis
- Myoglobinuric acute renal failure can result from rhabdomyolysis
- Iron
 - low serum iron concentration is commonly seen



Diagnostic Testing

- Additional testing
 - exclude structural brain disease and infection
 - **MRI/CT** - typically normal
 - **CSF** is usually normal
 - **EEG** generalized slow wave activity



DIFFERENTIAL DIAGNOSIS

- Serotonin syndrome
- Malignant hyperthermia
- Malignant catatonia
- Central nervous system infection (eg, meningitis, encephalitis)
- Systemic infections (eg, pneumonia, sepsis)
- Seizures
- Acute hydrocephalus
- Acute spinal cord injury
- Heat stroke (neuroleptics predispose to heat stroke by impairing thermoregulation)
- Acute dystonia
- Tetanus
- Central nervous system vasculitis
- Thyrotoxicosis
- Drug intoxication, toxicity (eg, phencyclidine, ecstasy, cocaine, amphetamines, lithium)
- Withdrawal states
- Acute porphyria



TREATMENT

- **Supportive care**
 - admission to the ICU is required.
 - Discontinue any neuroleptic agent or precipitating drug.
 - Maintain cardiorespiratory stability.
 - Mechanical ventilation, antiarrhythmic agents, or pacemakers may be required
 - **Maintain euvolemic state**
 - intravenous fluids.
 - Insensible fluid loss (fever and diaphoresis)
 - high volume intravenous fluids with urine alkalinization (rhabdomyolysis)

TREATMENT

- **Supportive care**
 - **Lower fever**
 - cooling blankets
 - ice water gastric lavage
 - ice packs in the axilla
 - acetaminophen or aspirin may have a role in reducing temperature in NMS, but it is not established
 - **Lower blood pressure**
 - if markedly elevated
 - Clonidine is effective in this setting
 - Nitroprusside may have advantages by also facilitating cooling through cutaneous vasodilation
 - **Heparin / LMWH**
 - prevention of DVT
 - **control agitation**
 - Use benzodiazepines if necessary



TREATMENT

- **Complications** are common and severe, even fatal. These include:
 - Dehydration
 - Electrolyte imbalance
 - Acute renal failure associated with rhabdomyolysis
 - Cardiac arrhythmias including torsades de pointes and cardiac arrest
 - Myocardial infarction
 - Cardiomyopathy
 - Respiratory failure from chest wall rigidity, aspiration pneumonia, pulmonary embolism
 - Deep venous thrombophlebitis
 - Thrombocytopenia
 - Disseminated intravascular coagulation
 - Deep venous thrombosis
 - Seizures from hyperthermia and metabolic derangements
 - Hepatic failure
 - Sepsis



TREATMENT

- **Medical therapy**
 - Recommendations are based upon case reports and clinical experience, not upon data from clinical trials.
- **Dantrolene**
 - direct-acting skeletal muscle relaxant
- **Bromocriptine**
 - a dopamine agonist
- **Amantadine**
 - dopaminergic and anticholinergic effects
- **Other medications**
 - levodopa
 - apomorphine
 - carbamazepine
 - benzodiazepines (lorazepam or clonazepam)

PROGNOSIS

- Most episodes resolve within **two weeks**.
 - mean recovery: 7-11 days
 - Cases persisting for six months with residual catatonia and motor signs are reported
- Risk factors for a **prolonged course**
 - depot antipsychotic use
 - concomitant structural brain disease
- Most patients recover without **neurologic sequelae** except
 - severe hypoxia
 - grossly elevated temperatures for a long duration.
- **Mortality**
 - **10-20%**
 - **Disease severity / medical complications** - the strongest predictors of mortality
 - increased in
 - myoglobinuria and renal failure versus control (18.8%→50%)
 - organic brain disease including alcohol and drug addiction – 38.5%
 - lower mortalities - with higher potency versus lower potency agents.



Our patient..

- Treated with Amantadine, LMWH, and supportive care.
- Rapid improvement
- Discharged at day 14.