Tropical Case Studies:
Febrile Coma &
Febrile Abdominal Pain

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Disclosures

- Relevant Financial Relationships
  - None

- Off-label Usage
  - None
Learning Objectives

- Differential diagnosis of the common presentation of the comatose febrile child in the tropics
- Management of the common illness that presents this way.
- Differential diagnosis of the febrile acute abdomen in the tropics
- Management of fever and abdominal pain in the tropics.
A Febrile Unconscious Girl

History:

- 2 ½ year old girl
- Fever x 4 days, dry cough, diarrhea, not eating x 1 day.
- Given a shot of “something” yesterday
- Worse yesterday pm, “asleep with eyes open”. Jerking arm movements a few hours ago.
A Febrile Unconscious Girl

PE: ~10 kg  T 39.4 °C, RR 40, Jaundiced
HEENT: Conjunctiva (and palms) markedly pale
NECK: +JVD, +HJR, supple.
LUNGS: bibasilar rales w/ Kussmaul’s resp. and intercostal retractions
COR: tachycardic w/ 2/6 SEM
ABD: soft w/ liver 3 FB’s and spleen 5 FB’s ↓
NEURO: coma w/ dysconjugate gaze, decerebrate opisthotonic posturing, hyperreflexia. SKIN: no rash
Opisthotonic (Decerebrate) Posturing
What is her diagnosis?

1. Malaria
2. Meningitis
3. Encephalitis
4. Typhoid Encephalopathy
5. Tetanus
6. Brain abscess
T - trauma either accidental or non-accidental
I - infection including meningitis/encephalitis/sepsis
P - psychogenic (might be considered in adolescents)
S - seizures or a post-ictal state
S - shunt including congenital heart disease, space-occupying lesions, or V/Q mismatching in pneumonia
A - abuse
E - electrolyte disturbances including hypoglycemia, dehydration, and metabolic disorders
I - intussusception (some children present with only vomiting and lethargy)
O - overdose (alcohol, other)
U - uremia
Meningitis

- Neck supple (meningeal signs often absent in HIV, young children)
- No rash
- Is there an epidemic?
- Maybe meningitis
- LP? But focal neurologic findings
Encephalitis

- Rabies
- Japanese encephalitis
- West Nile encephalitis
- Trypanosomiasis (sleeping sickness)
  - Need to diagnose to treat
  - Chronic
- Herpes Simplex encephalitis
  - Can’t diagnose most places/consider covering
Typhoid (Enteric) Fever

- CNS symptoms frequent in typhoid
  “typhoid encephalopathy”
  - “Toxic” staring apathetic appearance
  - Delirium
  - Aphonia
  - Stupor
  - Deafness
  - Encephalitis
  - Transverse myelitis
**Typhoid: Natural Course**

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- **Day -15**: 37°C
- **Day 0**: 40°C
- **Day 7**: ...
- **Day 21**: ...
Opisthotonic (Decerebrate) Posturing = Tetanus?
Tetanus

- Doesn’t cause coma
- Posturing happens during spasms of opisthotonus with trismus/risus sardonicus
- Diagnose with “The Spatula Test”

Brain Abscess

- Fever, headache, focal weakness
- Exam focal paresis
- LP for diagnosis? (removed)
- CT if available
- Treatment – Burr hole drainage
Brain Abscess
An Unconscious Little Girl

HPI: 2 1/2 y.o girl with fever x 4d, dry cough, diarrhea, not eating x 1d. Given a shot of “something” yest am at a dispensary. Worse since yest pm, not talking, asleep with eyes open. Jerking arm movements a few hours ago for a few minutes, not since.

PE: ~10 kg VS: T 39.4 C, RR 60 Jaundiced

GEN: Nasal flaring and intercostal retraction

HEENT: Conjunctiva markedly pale

NECK: +JVD, +HJR, supple.

LUNGS: bibasilar rales w/ Kussmaul’s resp.

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NEURO: coma w/ dysconjugate gaze, posturing, hyperreflexia. SKIN: no rash

= Malaria

+ = Severe (Cerebral?) Malaria
Malaria Diagnosis (WHO)

- Malaria (in Africa) if
  - Fever
  - Pallor
  - Splenomegaly
Tropical Febrile Coma

Labs:

\( \times \)

Shoot first, ask questions later!

(or concurrently)
Rx: Tropical Febrile Coma

- Oxygen, if available
- IV access
  - Try peripheral IV
  - If > 1-2 min, **Intraosseus needle!**
  - Draw blood sample
- IV glucose **stat**
Rx: Tropical Febrile Coma

15 Second Access - Intraosseus Needle Insertion

- Pillow under knee
- Prep anterior medial proximal tibia
- Insert with twisting motion a 16-18 g needle on luer lock syringe
- Feel pop or loss of resistance
- Flush and infuse
  - Can aspirate for CBC, malaria slide, crossmatch
Dx: Tropical Febrile Coma

Labs:
- Hematocrit 12%
- WBC 12,000 w/ left shift
- Thick smear ++++ Plasmodium falciparum (~20% parasitemia)
- Glucose (38 mg/dl)
Thin Smear
Diagnosis

- Severe malaria with severe anemia due to hemolysis, hyperparasitemia, pulmonary edema, hypoglycemia, lactic acidosis, and cerebral malaria
WHO Severe Malaria Criteria

- Cerebral malaria
- **Severe normocytic anemia** (Hgb<5 mg/dl endemic or <8 mg/dl in non-endemic area)
- Renal failure
- **Hyperparasitemia** (>20% endemic or >2% non-endemic)
- Pulmonary edema
- Hypoglycemia (glucose <40 mg/dl)
- Circulatory collapse
- Spontaneous bleeding/DIC
- Repeated generalized **convulsions**
- **Metabolic acidosis**
- Hemoglobinuria (blackwater fever)
- Prostration, severe weakness
- **Jaundice**
- Hyperpyrexia)
Rx: Severe Malaria

- IV Whole blood 30 ml/kg (+/- Lasix)
- Artesunate IV/IM 2.4 mg/kg at 0, 12, 24 & 48 hrs then daily (or PR or IM Artemether)
  - OR -
- Quinine 20 mg/kg IV loading dose over 4 hours then 10 mg/kg over 4 hours every 8 hours x 2 days then drop dose by ½.
Rx: Severe Malaria

- **IV Artesunate** drug of choice in adults (vs Quinine)
- Reduced risk of death
- No difference in
  - neurological sequela
  - coma recovery time
  - time to hospital discharge
  - fever clearance time
  - adverse effects except hypoglycemia.

Rx: Severe Malaria

- Check glucose q 2 – 4 hr.
- Tylenol
- Protect airway – nurse on side
- Diazepam for seizures; not phenobarbital.
- **Chloramphenicol** 50 mg/kg/day IV divided every 6 hours for 2 days (empiric treatment of sepsis/meningitis), then consider LP later.
Should I Do an LP?

- Focal neurologic defects and posturing
  - High risk of herniating...so no LP.
- I don’t know if she has meningitis?
- Will it change my treatment?
To LP or WHEN to LP…
(in the febrile, unconscious child in the tropics)

- Malaria (−) often is meningitis (in febrile coma in Kenya ~ 1/3)
- Malaria (+) can still have meningitis or sepsis too
- LP WBC (+) may be cerebral malaria only
- LP WBC (−) may have sepsis (though risk may not be lowered with empiric antibiotic)

- LP in acute meningitis is risky (5% meningitis herniates, cause of 30% of deaths, often temporally assoc. with LP)

- Don’t LP; treat with empiric antibiotics.

To LP or WHEN to LP...
(in the febrile, unconscious child in the tropics)

- Empiric antibiotics indicated either way because of difficulty distinguishing invasive bacterial infections from cerebral malaria.

Indications for an LP

- All patients with suspected CNS infection except those with:
  - Obtunded state with hypotension
  - Deep coma/responsive only to pain
  - Focal neurologic signs
  - HTN and bradycardia
  - Recent seizure (30 min)
Discharge Planning in Malaria

- Oral artesunate (or quinine)
- Long acting anti-malarial.
- Bednet.
- LP if not clearly cerebral malaria
- Counsel about neurologic sequelae (10-25%).
Artemisinin Combination Therapies

- Give combination med prior to discharge

  - Option 1: 3 days Artesunate (Quinine) +
    - Amodiaquine
    - Fansidar
    - Lumefantrine (CoArtem; Riamet),
    - Mefloquine (Use with Artesunate *not Quinine*)
    - (Malarone - $).

  - Option 2: 7 days Artesunate (Quinine) +
    Clindamycin or in children age>8
    Doxycycline +
Pull out, Steve, pull out... You've hit an artery!
Malaria & Global Health

- 2,000,000 deaths per year (leading cause among children < 5 yo)
- 90% of world cases in sub-Saharan Africa
- 1 in 5 childhood deaths in Africa
- 1/3 of deaths preventable with bed nets.
In areas of moderate to high malarial endemicity, febrile coma is usually cerebral malaria, but may be meningitis.

- Hypoglycemia is common
- Treat with Artesunate (or Quinine)
- Add a combination med prior to d/c.
- Bednets prevent death.
Malaria References

- WHO 2000: Management of Severe Malaria; accessed at http://apps.who.int/malaria/docs/hbsm.pdf The best resource on line for management of this common problem in the tropics!
Case 2: Learning Objectives

- To learn the differential diagnosis of acute abdomen in the tropics
- To learn to manage a syndrome of fever and abdominal pain in the tropics through case study.
Febrile Abdominal Pain in Tropics

HPI: 12 yo girl; HA, F x 2 weeks, abdominal pain x 1 week, severe 3 days.

ROS: cough, ST, constipation initially now thick green diarrhea 3 days.

PE: T: 39C  GEN: not in distress, diaphoretic.
    HEENT: no jaundice, mild pallor, mucous membranes dry, eyes sunken.  SKIN: Dry, tenting; no rash
    LUNGS: CTA  HEART: Tachycardia
    ABDOMEN: markedly distended with peritoneal signs, no mass, no hepatosplenomegaly, no bowel sounds.
    Percussion tympanitic.

Labs: thick smear Pf+, WBC 6,500 w/85% N, HCT 24%
What is the Diagnosis?

1. Amebic dysentery
2. Leptospirosis
3. Bacillary dysentery (Shigella)
4. Typhoid Fever
5. Malaria
Key Findings

History
- Long prodrome of F/HA
- Constipation changing to pea soup diarrhea
- Abdominal pain

Exam
- Peritoneal signs in RLQ
Differential of Fever, Headache, Abdominal Pain in the Tropics

Lack the prodrome:

- Appendicitis – less common in tropics.
- Intussusception
- *Amebiasis* – bloody diarrhea; less systemic.
- *Bacterial dysentery* – more GI symptoms; blood.
- Extrapulmonary TB (ileal)

Lack the acute abdomen:

- Pyelonephritis, Viral Hepatitis, Pneumonia, *Malaria*, *Dengue*, Influenza, Mono, Tularemia
What is the Diagnosis?

1. Amebic dysentery
2. Leptospirosis
3. Bacillary dysentery (Shigella)
4. Typhoid Fever with perforation
5. Malaria
Diagnosis

Typhoid (enteric) fever w/perforation
Severe dehydration
Malaria parasitemia (disease too?)
Complications of Typhoid

- CNS: Encephalopathy, psychosis, myelitis
- Cardiovascular: Myocarditis
- Pulmonary: Pneumonia
- **Gastrointestinal**
  - Perforation
  - Hemorrhage
  - Cholecystitis
  - Hepatitis
- **Chronic carriage**

Typhoid Fever
(status period: day 7-21)

- Sustained high fever, headache
- Apathy
- Constipation changing to diarrhea, abdominal pain
- HS’megaly

www.worldortho.med.usyd.edu.au
Natural Course of Typhoid

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- Incubation period: Days -15 to 0
- Invasion phase: Day 0
- Status period: Day 7
- Evolution: Day 21

Temperature:
- 37°C
- 40°C
Labs: Typhoid?

Tests of little help in most places in tropics:

- WIDAL
- X-Ray
- Culture (blood, stool, urine culture, bone marrow aspirate)
- PCR
- Typhidot
Typhoid Perforation

- **Rx:**
  - IV NS bolus
  - Foley
  - Chloramphenicol IV
    - Rocephin/Flagyl or Cipro/Flagyl
    - Azithromycin + Rocephin/Flagyl in SE Asia
  - OR
Typhoid Epidemiology

- Fecal-oral
- Source: asymptomatic carriers/patients
- 16 million cases occur annually in the world.
- More than 600,000 deaths.
- 62% of the global cases in Asia
Typhoid Epidemiology
Typhoid Pathogenesis

- Ingestion -> stomach -> small intestine -> penetration of the mucosa -> ileal Peyer's patches / mesenteric lymph nodes
- Hematogenous spread (spleen, liver, BM)
- Inflammation
- Focal necrosis
- Perforation, bleeding
Typhoid Pathophysiology

Ingestion of S. typhi by host

- Invades through gut

- Colonizes liver, spleen, lymph nodes, peyer patches

- In gut epithelium:
  - Bacteria-mediated endocytosis (BME)
  - Type III secretion system

- Invades through gut
- Enters bloodstream and attacks rest of body

- Multplies within mononuclear phagocytic cells

- Inflammation and diarrhea

- Gallbladder

- Bile ducts

- In submucosa:
  - Macrophage receptor-mediated phagocytosis

- Infect other hosts

- Stool, urine

- Ulcers, peritonitis

- http://www.healthygenius.com

- http://kdcp.hallym.or.kr

- http://www.cs.rochester.edu

- http://www.gcarlson.com

- Apoptosis
Microbiology

- Unable to culture in most hospitals where it occurs.
- Salmonella typhi (also Salmonella paratyphi A, B, or C – same symptoms)
Salmonella enterica serovar typhi
Typhoid Key Findings

- **History**
  - Long prodrome of F/HA
  - Constipation changing to pea soup diarrhea
  - Abdominal pain

- **Exam**
  - Peritoneal signs in RLQ if perforation
Complications of Typhoid

- Bleeding (5% Asia, rarer in Africa)
- Perforation (1-3% Asia, 10% Africa)
Complications of Typhoid

- Typhoid encephalopathy > "toxic" staring, apathetic appearance, delirium, aphonia, and stupor
- Pneumonia, Bronchitis
- Myocarditis, Endocarditis, Pericarditis
- Cholecystitis, Hepatitis, Pancreatitis
- Pyelonephritis
- Multi-organ abscesses
Tropical Diseases with Relative Bradycardia

- Typhoid fever
- Legionnaires’ disease
- Psittacosis
- Typhus
- Leptospirosis
- Malaria
- Babesiosis
- Dengue
- Q Fever

- Yellow Fever
- Rocky Mountain spotted fever
- Noninfectious causes of relative bradycardia:
  - (1) beta-blockers
  - (2) CNS lesions
  - (3) malignant lymphoma
  - (4) factitious fever
  - (5) drug-related fever

Rose Spots

- Rarely seen in Africa. Sometimes in Asians (~10%)
- See in up to 25% of Caucasians.
- Appear in 2nd week; disappear in 3-4 days
Diagnostic Tests

- Widal ("febrile agglutinins") useful slightly
  - O capsular antibody acute
  - Negative first week
  - Positive during second week.
  - H capsular antibody prior infection; persist

- Cultures – Often not available; bone marrow best, then blood.
Typhoid Diagnosis

- Blood culture + 70-80% in 1st 2 weeks.
  - Stool & urine cultures + 45-75% during the 2nd-3rd week.
- Bone marrow culture + 85-95%
  - Useful in patients pretreated with antibiotics.
Typhoid Diagnosis

- The future for rural hospitals?
  - Typhidot
    - IgM and IgG
    - Sensitivity 92% specificity 99% (using blood culture as gold standard)
  - Available for 10 years but still not replaced Widal.

Typhoid Treatment Caveats

- Severe resource limitations – use Chloramphenicol, Amoxicillin, TMP/SMX.
- Fluoroquinolones (Cipro) if available (and if low resistance)
  - 100% effective after 5 days
  - Better than Rocephin.
- Azithromycycin for MDR in SE Asia
- FQ’s work faster; more rapid stool clearance


Drug Resistant Typhoid

Treatment Caveats

- Azithromycin 500 mg (10 mg/kg) for 7 days 82% effective in MDR (others rec 1 gm daily x 5 days) esp. SE Asia.

- (Chloramphenicol, Amp, TMP/SX) /FQ less sensitive Typhoid (vs 64% ofloxacin efficacy and 72% 7 days ofloxacin – 3 days azithromycin combo).

- Ceftriaxone or Cefixime another option

**Steroids?**

- **High** dose Dexamethasone
  - Severe Typhoid (delirium, obtundation, stupor, coma, or shock)
  - 3 mg/kg by slow IV over 30 minutes then 1 mg/kg every 6 hours x 8 doses. $$$$
- Hydrocortisone lower dose not effective.


Clinical Response (non-perf’d)

- Defervescence usually occurs < 4 days.
- Cure rates exceed 96% with FQ’s.
- Fewer than 2% develop persistent fecal carriage or relapse
- If chronic urinary carriage, think Schistosomiasis hematobium.
Clinical Response (non-perf’d)

- Chronic fecal carriers (asymptomatic excretion for ≥1 year) about 1-6%
- Norfloxacin 400 mg orally twice daily for 28 days was 86 percent if normal gallbladder, and 75 percent with gallstones
- Ciprofloxacin 500 or 750 mg orally twice daily for 14 to 28 days eliminated carriage in 90 to 93 percent of cases.

References