Leptospirosis and Typhoid Fever

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Colorado School of Public Health

November 2015
26 y/o gentleman with myalgia and shortness of breath

- Bilateral LE pain, headache, fever x 1 week
  - Cr 1.8, CPK 1465, Hct 42, Plt 96,000

- Returned to ED with shortness of breath and worsened myalgias
  - Cr 3.6, Hct 32, Plt 65,000

- ROS: wife and children with upper respiratory symptoms, no other sick contacts; poor PO intake
Outside Hospital Course

- HD#2. Increased hypoxia necessitating intubation. Gross blood returned from endotracheal tube.
- Hypotension requiring pressor support.
- Methylprednisolone and cyclophosphamide started for presumed Goodpasture’s syndrome.
- CVVH and plasmapheresis started.
- Increased hypoxia with $\text{SaO}_2$ in the 80s despite maximal support.
Past Medical History

• None
<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>SOCIAL HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ibuprofen PRN</td>
<td>Lives in Denver with wife and two young children. Works as a waste collector.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FAMILY HISTORY</th>
<th>Tobacco: 1 ppd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for autoimmune disease, malignancy, renal disease, or coagulopathy.</td>
<td>Alcohol: Occasional</td>
</tr>
<tr>
<td></td>
<td>Illicit drugs: None</td>
</tr>
</tbody>
</table>
Physical Examination

VS: 36.2  136/82  97  on Vasopressin
Gen: intubated, sedated, obese, jaundiced
HEENT: scleral icterus, ETT in place
Chest: mildly coarse throughout
CV: RRR, no m/r/g, normal JVP
Abd: +BS, soft, NT, no hepatosplenomegaly
Ext: no clubbing, cyanosis, edema, 2+ pulses
Neuro: pupils 2 mm & sluggish, +gag, withdraws all extremities to pain, symmetric reflexes
Skin: PICC in RUE without erythema
<table>
<thead>
<tr>
<th></th>
<th>AST 477</th>
<th>ALT 198</th>
<th>Alk Phos 36</th>
<th>T Bili 22.7</th>
<th>T Prot 4.9</th>
<th>Alb 2.9</th>
</tr>
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<tbody>
<tr>
<td>138</td>
<td>2.7</td>
<td>7.7</td>
<td>9.9</td>
<td>179</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>4.2</td>
<td>9.9</td>
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<tr>
<td>AG 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.6</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
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</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Diff: 4.5 poly, 0.7 lymph, 0.96 mono, 0.38 bands

ABG: 7.27/62/80/27 on 100%

UA: 2+prot, +bili, 3+blood, 2+WBC, 1+RBC, 1+cellular cast, 1+granular cast
Hospital Course

- Continued on broad-spectrum antibiotics: vancomycin, ceftriaxone, azithromycin, doxycycline
- Continued on methylprednisolone
- Plasmapheresis and IVIG for possible autoimmune pulmonary hemorrhage
- Further Labs:
  - ANA neg, anti-ds DNA neg, ASO neg, C3 normal, C4 slightly low
  - Anti-GBM neg, P-ANCA neg, C-ANCA neg
  - Leptospira titer 1:50 (borderline positive)
Hospital Course

• HD#3. Pulmonary status improved to allow bronchoscopy
  – Evidence of ongoing pulmonary hemorrhage.
  – Cultures negative for viral, bacterial, fungal pathogen
• Urine output improving off dialysis
• HD#7. Successful extubation
• Repeat leptospira titer 1:12,800
• HD#11. Discharged to home.
Leptospirosis with Severe Pulmonary Hemorrhage Syndrome
Leptospirosis

OBJECTIVES

• Review Basics
• Update on Diagnostic & Therapeutic Challenges
• Offer Practical Approaches

SLIDES

• Available to you
Zoonoses

Definition
• Infections shared between humans and other vertebrate hosts

Vertebrates Implicated
• Examples from virtually every class

Pathogens Transmitted
• Bacteria, Viruses, Fungi, Parasites, Prions

Clinical Spectrum of Disease
• May involve virtually any organ system
Zoonoses

Definition
• Infections shared between humans and other vertebrate hosts

Animals Implicated
• Virtually every class

Pathogens Transmitted
• Bacteria, Viruses, Fungi, Parasites, Prions

Clinical Spectrum of Disease
• May involve virtually any organ system

Shared Requirement for Diagnosis
History, History, History...
Labwork is confirmatory
1886: Weil

- Described 4 cases of scleral icterus & renal failure, earning monicker “Weil’s Disease.”

Other Names:

- Swineherd's disease
- Rice-field fever
- Cane-cutter fever
- Swamp fever
- Mud fever
- Hemorrhagic jaundice
- Stuttgart disease
- Canicola fever
Leptospirosis: History

1907: Stimson

- Autopsy pt with presumed yellow fever:
  - spirocetes in renal tubules on silver stain
  - hook at end looked like question mark, naming it “Spirochaeta interrogans”
Leptospirosis: History

1915: Noguchi & Stokes

• Renewed interest due to massive outbreaks in trenches of WWI.
• Simultaneous efforts in Japan & Germany demonstrate lethality of organism from animal urine.
• Both scientists die of leptospirosis acquired in lab.
Leptospirosis: Epidemiology

- Worldwide distribution

- 1,030,000 cases, 58,900 deaths worldwide
- ~200 cases/year reported in USA
  - 50% in Hawaii

- "Most common zoonosis on planet"
**Leptospirosis: Pathophysiology**

- Favorite hosts: rats, dogs, swine, cattle.
- Bacteria colonize kidneys → shed in urine.
- Enter new host via mucosa, abrasions, or possibly intact skin.
- Numerous genes for adhesion, invasion, and host damage recently discovered.
- Outcome varies greatly with serovar.
**Leptospirosis: Pathophysiology**

<table>
<thead>
<tr>
<th>T. pallidum</th>
<th>L. interrogans</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 1,000 ORFs</td>
<td>~ 3,500 – 4,500 ORFs</td>
</tr>
</tbody>
</table>
**Leptospirosis: Microbiology**

**Animals:** *Leptospira biflexa*

**Animals & Humans:** *Leptospira interrogans*

- > 200 serovars
- Left-handed spirochetes, > 18 coils
- Stain poorly with Gram Stain or H&E... best seen on silver stain or darkfield
- Aerobes
- Can be cultivated ex-vivo in special media (growth may take > 1 week)
Leptospirosis: At-Risk

Occupational Exposure
Farmers, ranchers, abattoir workers, trappers, veterinarians, loggers, sewer workers, rice field workers, military personnel, laboratory workers, garbage collectors.

Recreational Activities
Fresh water swimming, canoeing, kayaking, rafting, trail biking.

Household Exposure
Pet dogs, domesticated livestock, rainwater catchment systems, infestation by infected rodents.

Other
Skin lesions, contact with wild rodents.
Leptospirosis: At-Risk

When your patient has bathed in animal urine, think “Lepto!”
Leptospirosis: Clinical Illness

Incubation 2-26 days → “Influenza-Like Illness”

Majority:
- Fever
- Malaise
- Myalgias
- Spontaneous resolution & seroconversion

Minority:
- Abdominal pain
- Jaundice
- Scleral icterus
- Conjunctival suffusion
- Thrombocytopenia
- Hypokalemia
- Edema
- “Sterile” pyuria
- CK elevation
- Spontaneous resolution & seroconversion

“Biphasic” illness <50%!
### A “biphasic disease”

Separation often unclear!

<table>
<thead>
<tr>
<th>Septicemic phase</th>
<th>Immune phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>One to several days</td>
<td>Fever recurrence, rigors, headaches, prostration, myositis (high CK), rash, mono or polyarthritis, organ manifestations</td>
</tr>
<tr>
<td>Fever, conjunctival suffusion, myalgias, bradycardia, (+ cultures) hypotension, dehydration</td>
<td>Convalescence 6-12 w</td>
</tr>
<tr>
<td>Recovery 5d - 6w</td>
<td></td>
</tr>
</tbody>
</table>
**Leptospirosis: Complications**

- ARDS
- Hepatitis
- Renal failure
- Rhabdomyolysis
- Myocarditis
- Hemorrhage
- Uveitis
- GBS / ADEM / TM
- Death
Icteric leptospirosis

- Fever, jaundice and purpura

Always look at the eyes!

Raul Isturiz, MD
Conjunctival suffusion and hemorrhages, no conjunctivitis
Leptospirosis: DDX

- Influenza
- Dengue Fever
- Yellow Fever
- Malaria
- Salmonella typhi
- Rickettsiae (RMSF)
- Ehrlichiosis
- Acute viral hepatitis A or B
- Goodpasture’s Disease
Leptospirosis: Diagnosis

Direct Fluid Exam on Darkfield or Silver

😊 Instant results
😊 Hazardous to staff; low NPV

Culture

😊 Gold standard
😊 Fastidious requirements, may take 1-3 weeks

Serology

😊 Paired acute & convalescent titers very sensitive
   (> 4-fold rise or any titer > 1:800)
😊 Slow… pt dead or cured by time results back

PCR

😊 Experimental; PPV great, but NPV useless

Cross-Reactivity reported with
- Legionellosis (L.pneumophila)
- Lyme Disease (B.bergdorferi)
- Relapsing Fever (B.hermsii)
- Syphilis (T.pallidum)
Leptospirosis: Treatment

• **No Contest:** Meticulous supportive care.
• **Controversy:** Need for antibiotics?
  ✓ Most clear infection spontaneously
  ✓ Retrospective case series demonstrate inconsistent benefit.
  ✓ Note disease heterogeneity.
• **Consensus:** OK to Rx pts sick enough to seek care.
• **Caveat:** Watch for Jarisch-Herxheimer!
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leptospirosis</strong></td>
<td></td>
</tr>
<tr>
<td>Mild Disease</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 PO BID x 7 days</td>
</tr>
<tr>
<td>or</td>
<td>500 PO TID x 7 days</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
</tr>
</tbody>
</table>

Doxy Preferred: Less Herx, Also Covers *Rickettsiae*
<table>
<thead>
<tr>
<th>Leptospirosis</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Disease</td>
<td>Doxycycline</td>
<td>100 IV BID x 14 days</td>
</tr>
<tr>
<td>or</td>
<td>PCN-G</td>
<td>6 mu IV Daily x 14 days</td>
</tr>
<tr>
<td>or</td>
<td>Cefuroxime</td>
<td>500 PO BID x 14 days</td>
</tr>
<tr>
<td>or</td>
<td>Ceftriaxone</td>
<td>2 gm IV QD x 14 days</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-Line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PCN-allergic,</td>
<td>Azithromycin</td>
<td></td>
</tr>
<tr>
<td>cannot</td>
<td>500 x 1, then 250 QD x 14 d</td>
<td></td>
</tr>
<tr>
<td>desensitize)</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithro</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 PO BID x 14 d</td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>FQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X 14 d</td>
<td></td>
</tr>
<tr>
<td>Telithromycin</td>
<td>800 QD x 14 d</td>
<td></td>
</tr>
</tbody>
</table>
**Leptospirosis: Summary**

- **Zoonosis:** world’s most common
- **Cause:** spirochete *Leptospira interrogans*
- **Clinical manifestations:** Protean
  - (subclinical ↔ hepatorenal dz ↔ coma ↔ death)
- **Diagnosis:** High suspicion; serology; culture; PCR
- **Treatment:** Observation in mild cases vs. Empiric Doxy > β-lactam > FQ or macrolide; meticulous supportive care
- **Prevention:** Improved Sanitation
Leptospirosis: References


Case 2

- A 15 year-old boy complains of bloody diarrhea.
- Returned from a trip to Costa Rica.
History

• Spent a week in capital city of San Jose on vacation.
• Dined at restaurants and in friends homes.
• Stayed in a high rise hotel. No excursions out of town.
• Denies sexual activity while there.
• Stools turned “runny” on the third day there. Used imodium with some improvement for two days, then no benefit.

• Stool now foul-smelling, gelatinous, brown with some bright red blood on paper.

• Severe abdominal cramps with bm’s.

• Subjective fevers for last few days.
• **PMH:** Untreated HTN, elevated lipids
• **Vaccinations:** Childhood series unclear
• **Meds:** Imodium, APAP
• **Habits:** 20 pk/yr tobacco
• **FH:** None
Exam

- 38.1° / 92 / 130/90 / 20 / 166 lbs
- Appears exhausted, pale
- HEENT clear.
- No murmur, lungs clear, GU normal
- Hyperactive bowel sounds, diffusely tender to firm palpation, voluntary guarding, no HSM, engorged external hemorrhoids, minor rectal tenderness, small amount of maroon blood on glove
Labs in Clinic

- WBC 12.4 (nl diff), Hct 39, Plt 300
- First thick & thin smears negative
- Others pending
Quick Differential

Dysentery (blood or mucus in diarrhea), urban Latin America, mildly toxic now, normal host

- Campylobacter
- Salmonella enteritidis
- Shigella
- Clostridium difficile
- E. coli (EPEC & EHEC > ETEC)
- Yersinia enterocolitica
- Aeromonas, plesiomonas
- Entamoeba histolytica

- Malaria can cause diarrhea, but almost never dysentery… low exposure risk here
# Acute Diarrhea: Agents

<table>
<thead>
<tr>
<th></th>
<th>Small Bowel</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td><em>E. coli</em> (ETEC, EPEC), <em>Staphylococcus aureus</em>, <em>Clostridium perfringens</em>, <em>Bacillus cereus</em>, <em>Vibrio cholera</em>, <em>Salmonella</em>.</td>
<td><em>Campylobacter</em>, <em>Shigella</em>, <em>Salmonella</em>, <em>Clostridium difficile</em>, <em>Yersinia</em>, <em>EHEC (0157:H7)</em>, <em>Vibrio parahemolyticus</em>, <em>Plesiomonas shigelloides</em>, <em>Aeromonas hydrophila</em></td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Rotavirus, Norovirus, Astroviruses, Caliciviruses</td>
<td>Cytomegalovirus, Adenovirus</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td><em>Giardia lamblia</em>, <em>Cyclospora cayatenensis</em>, <em>Cryptosporidium parvum</em>, <em>Microsporidium sp.</em>, <em>Dientamoeba fragilis</em>, <em>Isospora belli</em>.</td>
<td><em>Entamoeba histolytica</em>, <em>Balantidium coli</em></td>
</tr>
</tbody>
</table>
Plan

Stool sample
Acute Diarrhea

When to Test?
Instructions:

1. Fold side flaps up and remove back from adhesive tape on both sides of collection container.

2. Insert container into toilet toward the back of the bowl. Attach tape to toilet seat and slip paper dish into shape. Have a bowel movement into collection container.

3. Scoop feces with scoop attached to tube lid. Fill tube to red fill line on label. Screw lid tightly. Complete both copies of label and stick to side of specimen tube.

Note: Do not flush specimen collection container.

Figure 2. Laboratory-confirmed etiologies of infections in 54 outbreaks in which stool collection kits were deployed.

Delivered Stool Kits in Outbreaks • CID 2004:39 (15 November)

<table>
<thead>
<tr>
<th>Reference, study</th>
<th>No. of cultures performed</th>
<th>Isolates recovered, % of cultures</th>
<th>Salmonella; Shigella; Campylobacter jejuni</th>
<th>STEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total 2.4</td>
<td>2.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>[33]</td>
<td>2468</td>
<td>2.4</td>
<td>2.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>[34]</td>
<td>2020</td>
<td>1.5</td>
<td>1.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
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<tr>
<td>[77]</td>
<td>1964</td>
<td>2</td>
<td>0.6; .2; 1.2</td>
<td>—</td>
</tr>
<tr>
<td>Ova and parasites</td>
<td>1423</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>2668</td>
<td>21</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>[78]</td>
<td>1800</td>
<td>2.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>[80]</td>
<td>30,463</td>
<td>5.6</td>
<td>1.8; 1.1; 2.3</td>
<td>0.4</td>
</tr>
<tr>
<td>[18]</td>
<td>233,212</td>
<td>3.2</td>
<td>0.9; 0.6; 1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Ova and parasites</td>
<td>217,886</td>
<td>2.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE  STEC, Shiga toxin–producing *Escherichia coli*.

<sup>a</sup> Cumulative percentages for isolates of all 3 organisms.

<sup>b</sup> *Cryptosporidium*, 1.7%; *Cyclospora*, 0.4%.
Acute Diarrhea: When to Test?

Initial Clinical Evaluation

- Duration of Symptoms
- Severity of Illness
- Exposures
- Comorbidities

< 48 hours
Acute Diarrhea: When to Test?

Initial Clinical Evaluation

- Duration of Symptoms
- Severity of Illness
- Exposures
- Comorbidities

- ✓ Volume Status
- ✓ Fever
- ✓ Severe abdominal pain
- ✓ Hematochezia
- ✓ Trending to worse
Acute Diarrhea: When to Test?

Initial Clinical Evaluation

- Duration of Symptoms
- Severity of Illness
- Exposures
  - Exotic travel
  - Camping
  - Group eating
  - Ill contacts / clusters
  - Recent antibiotics
  - Recent inpatient admission
- Comorbidities
Acute Diarrhea: When to Test?

Initial Clinical Evaluation

- Duration of Symptoms
- Severity of Illness
- Exposures
- Comorbidities

- HIV
- Cancer
- Immunosuppressants
- IBD
- Food handlers
- “Elderly or infirm”
Acute Diarrhea

What to Send?
Fecal WBCs

- NPV ≈ 50%
- PPV ≈ 70%

Fecal lactoferrin

- NPV ≈ 90%
- PPV ≈ 99%

Routine Culture

- NPV ≈ 90%
  - Salmonella
  - Shigella
  - Campylobacter

Process ASAP!

Wanke CA. UpToDate.com
Initial assessment
Evaluate for: Dehydration, Duration, and Inflammation (Fever, blood in stool)

Symptomatic therapy
(hydration, alteration of diet)

Severe illness — hypovolemia, bloody stools, fever, ≥6 unformed stools per 24 hours, duration >48 hours, severe abdominal pain, elderly (age ≥70 years), or immunocompromised

Yes

No

Illness continues
Illness resolves

Test for fecal leukocytes
Routine stool culture
Consider nonroutine stool culture or ova and parasites in select situations (see text)
Consider C. difficile if recent antibiotic therapy

Inflammatory
(eg, Campylobacter, Shigella, Salmonella, Entero-hemorrhagic E. coli, C. difficile)

Consider empiric therapy while awaiting culture results in the following groups: patients with fever or bloody diarrhea; patients with >8 stools per day, dehydration, symptoms >1 week, immunocompromised, if hospitalization considered.

Noninflammatory
(eg, Norwalk, Rotavirus, C. perfringens, S. aureus, B. cereus, Giardia, drugs, occasionally IBD)

Continue symptomatic therapy
Further evaluation if symptoms persist

Consider specific therapy once pathogen identified (see text for indications, type of treatment)
One Routine Stool Culture... $161.50

Knowing your patient’s pathogen... priceless?
598 Adult Swedes with acute diarrhea randomized to norfloxacin 400 PO BID v. placebo

- 51% had pathogens on stool cx
  (29% campy, 16% salmonella, etc.)
  - Overall time to “cure” with abx 1.7 days v. 2.8 days
  - Among “severely ill,” time to cure 1.5 v. 3.4 days
  - Salmonella clearance less likely with abx at 2 weeks (18% v. 49%)
  - No kids included, no O157:H7
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>First choice</th>
<th>Second choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>Not required</td>
<td>Not required</td>
<td>Due to food poisoning and resolve with hydration only. TMP/SMX* can be used if susceptible; antibiotic therapy required only in severe cases (see text)</td>
</tr>
<tr>
<td>B. cereus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>Usually not required (see text)</td>
<td>Oral quinolone† BID for 3 to 5 days</td>
<td>Same as above</td>
</tr>
<tr>
<td>Shigella</td>
<td>Oral quinolone† BID for 5 days</td>
<td>TMP/SMX* or ampicillin</td>
<td>Many strains now resistant to TMP/SMX* and ampicillin</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Oral quinolone† BID for 5 days</td>
<td>Macrolides¶ or doxycycline</td>
<td>Antibiotics only in severe cases (see text). Quinolone resistance has been reported</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Oral quinolone† BID for 7 to 10 days</td>
<td>TMP/SMX* or doxycycline</td>
<td>Antibiotic therapy only in severe (systemic) cases</td>
</tr>
<tr>
<td>C. difficile</td>
<td>Metronidazole 250 mg PO QID</td>
<td>Vancomycin 125 mg PO QID</td>
<td>Duration of therapy 10 days; stop antibiotics, if possible; IV metronidazole if unable to tolerate oral therapy; IV metronidazole ± vancomycin fecal enemas for severe cases</td>
</tr>
<tr>
<td>ETEC</td>
<td>Oral quinolone† BID for 1 to 3 days</td>
<td>TMP/SMX*, doxycycline, furazolidone</td>
<td></td>
</tr>
<tr>
<td>EIEC</td>
<td>Same as for Shigellosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHEC</td>
<td>Not recommended at this time</td>
<td>? oral quinolone†</td>
<td></td>
</tr>
<tr>
<td>V. cholerae</td>
<td>Oral quinolone</td>
<td>Doxycycline</td>
<td></td>
</tr>
</tbody>
</table>

*Trimethoprim/sulfamethoxazole 160/800 mg (DS tab) PO q 12 h
† Norfloxacin 400 mg PO, ofloxacin 400 mg PO, ciprofloxacin 500 mg PO
¶ Erythromycin, clarithromycin, azithromycin
Dysentery: Pearls

• Antimotility agents should be avoided: “let it flow.” If you gotta use them, titrate to several stools / day.

• Probiotics *Lactobacillus* and *Saccharomyces* won’t hurt (unless neutropenic), and may help. “BRAT” diet of questionable value.

• For travelers, prophylaxis with bismuth subsalicylate 2 tabs PO QID leads to ~60% reduction in diarrhea.
A Randomized, Double-Blind, Placebo-Controlled Trial of Rifaximin To Prevent Travelers’ Diarrhea

Herbert L. DuPont, MD; Zhi-Dong Jiang, PhD; Pablo C. Okhuysen, MD; Charles D. Ericsson, MD; Francisco Javier de la Cabada, MD; Shi Ke, MD; Margaret W. DuPont, MA; and Francisco Martinez-Sandoval, MD, PhD

Background: Travelers’ diarrhea causes substantial morbidity and postinfectious irritable bowel syndrome.

Objective: To evaluate nonabsorbable rifaximin for prevention of travelers’ diarrhea.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: Guadalajara, Mexico.

Participants: U.S. students.

Intervention: On arrival in Guadalajara, Mexico, 210 U.S. adults received rifaximin (200 mg/d, 200 mg twice daily, or 200 mg 3 times daily) or placebo for 2 weeks.

Measurements: Participants were followed daily for 3 weeks for enteric disease and symptoms and daily for 5 weeks for drug side effects. Changes in intestinal coliform flora were studied.

Results: Travelers’ diarrhea developed in 14.74% of participants taking rifaximin and 53.70% of those taking placebo (rate ratio, 0.27 [95% CI, 0.17 to 0.43]). Rifaximin provided 72% and 77% protection against travelers’ diarrhea and antibiotic-treated travelers’ diarrhea, respectively (P < 0.001 for both), and all rifaximin doses were superior to placebo. In the groups that did not report travelers’ diarrhea, rifaximin significantly reduced the occurrence of mild diarrhea (P = 0.02) and moderate and severe intestinal problems (P = 0.009 for pain or cramps; P = 0.02 for excessive gas). Rates of adverse events were comparable in the rifaximin and placebo groups. Minimal changes in coliform flora were found during rifaximin therapy.

Limitations: Rifaximin safely prevented travelers’ diarrhea in Mexico, where most cases are caused by diarrhea-producing Escherichia coli. A study is needed in Asia to determine whether rifaximin can prevent diarrhea caused by invasive bacterial pathogens.

Conclusions: Rifaximin prevents travelers’ diarrhea with minimal changes in fecal flora, and more liberal chemoprophylaxis against this disease should be considered. Future studies should evaluate whether rifaximin is effective in preventing postinfectious irritable bowel syndrome.
Plan

Several valid approaches

• Emphasize supportive care / hydration
• No admission or abx mandatory unless he becomes more “toxic” or symptoms > 1 week
• Many MD’s will send a culture / O&P, though usually will not change approach
Followup

Stool cultures come back: *S. enterica serovar typhi*

Three major scenarios with this bug

• Asymptomatic carriage
• Enteric fever
• Typhoid fever, with or without metastatic spread
TYPHOID ≠ TYPHUS

*S. Typhi* (fecal / oral)  
*Rickettsiae* (louse, flea, tick, mite)

Names for both come from Latin for “fog” because both can cause delirium with high fevers.
“Typhoid Mary” Mallon

• Irish immigrant, worked as a cook in NYC.
• Felt well… first asymptomatic carrier found in US.
• 1907-1915 infected 47 and killed three.
• Forcibly quarantined on island in East River x 26 years… never cured.
Salmonella → Entry → Adherence → Columnar epithelial cells of the small intestine → Penetration → Lamina propria → Multiplication → Systemic dissemination → Deep tissue invasion → Phagocytosis by neutrophils and macrophages → Secretion of water and electrolytes → Diarrhea
Salmonella typhi and Typhoid Fever

• World-wide incidence ~ 12.5 million cases / yr
• Hospital-based mortality in developing world 1-30%
• Outpt mortality in developed world ~1%
• Most cases imported from travelers to Mexico and Indian subcontinent
• About 5,000 U.S. cases annually
Rose Spots
Salmonella typhi and Typhoid Fever

- Incubation generally 7-14 d (range 3-60 d)
- Fever 99%
- Headache 85%
- Hepatomegaly 50%
- Abdominal pain 45%
- Diarrhea 45%
- Rose spots 0-50%
- Splenomegaly 35%
- Disorientation 15%, Delirium 10%, Stupor 2%
- Relative bradycardia 15%
Complications of Typhoid Fever

- Intestinal perforation & hemorrhage
- Renal failure
- Pneumonia & ARDS
- Myocarditis & CHF
- Shock
- Meningitis
- Abscesses
- Arthritis
- Osteomyelitis
- Aneurysms
- Cholecystitis
Salmonella typhi and Typhoid Fever Prevention

- IM Vaccine: “Typhim VI”
  - Boost: After 2-3 years
  - Cost: ~$50-70

- PO Vaccine: “Vivotif”
  - Boost (repeat series): 5 years
  - Cost: ~$50-70
Salmonella typhi and Typhoid Fever Prevention

CAVEATS

✓ Efficacy likely 50-70%
✓ PO vaccine may provide superior protection
✓ IM vaccine currently in short supply
✓ No protection from paratyphoid fever
Salmonella typhi and Typhoid Fever

Diagnosis

- Bone marrow aspiration most sensitive (95%), but rarely performed
- Culture of blood (40-80%) duodenal secretions (60-80%) and stool (30-50%)
  - Together ~85% sensitive
- Widal’s test (poor PPV and NPV)
Salmonella typhi and Typhoid Fever

Therapy

- Quinolones (14 days)
- Chloramphenicol, TMP/SMZ, ampicillin, 3rd generation cephalosporins (7-10 days after defervescence)
- Multi-drug resistant S. typhi increasingly widespread
- Patients with severe typhoid fever (delerious, obtunded, stuporous, comatose, in shock) should receive steroids

Azithromycin Drug of Choice
Non-Typhi Salmonella (NTS)

A Newly-Appreciated Issue

• Classic Belief: Gives you the squirts, nothing more.
• Now Understood: Many children presenting to casualty in SSA have NTS bacteremia and sepsis....
• Typically, they are treated for malaria (common, diagnosable, and treatable)
• Work of Dr. John Crump & Colleagues in Tanzania very instructive
Salmonellosis: Key Clinical Concepts

**Agent:** Salmonella enterica… serovar typhi and paratyphi may lead to typhoid fever. Non-typhi salmonella may cause dysentery… or sepsis!

**Epi:** Incredibly common worldwide.

**Dx:** Check the poop, blood, marrow.

**Rx:** Abx… FQ’s no longer reliable!

**Prevention:** Sanitation! IM and PO vaccines for typhi also available.


