Shiga Toxin-Producing *Escherichia coli*: The Human Health Perspective

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NOTE: Some slides could include data that have not yet been published, or subject to peer review, and should not be quoted and should be considered to be preliminary.
Perspective

*E. coli* O157:H7: ~ .9/100,000 people/year

(MMWR Morb Mortal Wkly Rep 2011;60:749-55)

HUS: 500-750 cases per annum, 90% < 18 yo

Rare infections need good systems, protocols, and vigilance
• How can we optimally diagnose this infection?

• Can we attenuate human illnesses?

• What misconceptions do we need to address?
Time is not on your side!
First Contact (frequently ER)

Profile:

<table>
<thead>
<tr>
<th>Table 1. Elements at Presentation That Suggest a Patient Is Infected With E coli O157:H7</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nonbloody diarrhea that becomes bloody after 1–3 days.</td>
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<tr>
<td>• No fever at presentation to medical care.</td>
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<td>• Tender abdomen.</td>
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<tr>
<td>• More than 5 stools in the past 24 hours.</td>
</tr>
<tr>
<td>• Pain is worse on defecation.</td>
</tr>
<tr>
<td>• No, few, or moderate fecal leukocytes (but fecal leukocytes, in our opinions, have little relevance in this situation).</td>
</tr>
<tr>
<td>• Diarrhea, and especially bloody diarrhea, persists during first 8 hours in hospital.</td>
</tr>
<tr>
<td>• There is no relative bandemia in the differential white cell count.</td>
</tr>
</tbody>
</table>

Memorial Day to Thanksgiving

Strategic Microbiology

• Culture! 
  \((C. \text{ difficile} \text{ optional} – \text{ await bacterial culture})\)

• Hustle stool to the lab
First Medical Contact

Microbiologic Evaluation is CRITICAL
Microbiologic Evaluation is Critical

Agar vs. Assay

- Stool
- Broth
- Incubate O/N
- Shiga Toxin EIA
Agar detects only O157:H7, but this single serotype remains the nearly exclusive (>95%) cause of HUS in US, UK, Canada, Japan, and South America

Pediatrics. 1987;80:37
J Infect Dis. 1990;162:553
J Pediatr. 1998;132:777
J Infect Dis. 2001;183:1063
J Pediatr. 2002;141:172
Foodborne Pathog Dis. 2006;3:88
Epidemiol Infect. 2007 Mar 5 (epub)1-7
How much HUS do non-O157:H7 STEC cause in US?

83 patients with HUS, (1987-91), nationwide surveillance (Banatavala, et al*).

70 patients had stool cultures with growth, median of 8 days after illness onset.

30 patients had STEC; 25 of these were O157 (overall O157 rate: 35%)
(only 1/3 of HUS patients have O157:H7 if cultured on admission with HUS**, but 96% are + if cultured early in illness)

Of 5 patients from whom non-O157:H7 STEC were recovered, 4 had serology, and 3 of these 4 had evidence of a recent infection with *E. coli* O157.

Of 31 cases from whom no STEC were recovered, 21 had antibodies to O157.
(Sera obtained up to 80 days after illness onset, well after seropositivity peak***, so this rate is possibly low.

Little room left for non-O157:H7 STEC to cause HUS in US

Recent Study of HUS

50 children with diarrhea – associated HUS, from 10 centers in US (UC Davis, Seattle, Indiana, Little Rock, Milwaukee, Albuquerque, Columbus, Cincinnati, St. Louis) and 1 in Scotland (Glasgow) (Hickey, et al*)


27+ for O157, 1 + for O121:H19, All other were negative

*Arch Pediatr Adolesc Med. 2011;165:884

663 STEC infections

271 (41%) O157 culture isolates

392 (59%) Shiga toxin (+) broths

163 (42%) O157 STEC

229 (58%) non-O157 STEC

30 serogroups


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Connecticut 2000-2009

- 499 broth + EIAs
- 163 were O157:H7 (33%)
  - 10% HUS rate
- 229 were non-O157:H7 STEC (46%);
  - 0.4% HUS rate
- 78 (16%) were not + at State Laboratory
- 29 (6%) no STEC recovered

Clin Infect Dis 2011;53:269
O157/non-O157 Acuity Pyramid
HUS 95/5 - 99/1 in multiple studies

Seattle Children’s Hospital Emergency Room
1991\(^1\): 13/5
1998-2001\(^2\): 28/11

Statewide, MT (1998-2000)\(^3\) and CT (2000-2009) \(^4\)
MT: 32/50 (#2 was O26, with 16 isolates)
CT: 163/229 (#2 was O111, with 44 isolates)

Toxin Screening misses O157:H7 (i.e., sorbitol MacConkey agar is more sensitive)

- Klein, E, et al, J Peds 2002; 172;
Toxin Assays Slow Diagnosis of O157:H7

- Not read daily in many centers
- Often sent to commercial laboratories
- Isolation devolves to state PHL
- State of isolation isn’t always state of presentation or residence
- Specimen transport issues
Why rapidly diagnose O157?

- *E. coli* O157:H7 → thrombotic complications, epidemics; other serotypes rarely do

- Syndromic profiling helpful, but clinician needs + or - culture result ASAP

- HD needs isolate

- Intervention appears possible
Best Practices - Microbiology

Plate 24/7, don’t wait for morning shift, swabs are fine

Report presumptive positives

Receipt to telephone call:
23 hr, 53 min (14 – 56 h)
CDC Guidelines

Recommendations for Diagnosis of Shiga Toxin--Producing Escherichia coli Infections by Clinical Laboratories


“All stools submitted for testing from patients with acute community-acquired diarrhea … should be cultured for O157 STEC on selective and differential agar.”

Best practice: Agar and toxin assay

What’s the rush?
↑D-dimer Before HUS

NEJM 2002; 346:23
Child at Presentation

- Little or no toxin in stool
- Coagulation system activated, but CBC normal
- Pathogen still present in stool
- Kidneys not yet injured

What’s a provider to do?
Admit, Isolate

Inpatient (contact) precautions:
dedicated equipment, gowns, gloves

Outpatient advice:
“Wash your hands well!”

Withhold antibiotics

1997-1999, n=71

OR

• Antibiotics are a risk for HUS in MN
  Smith, K, et al, Pediatr Infect Dis J. 2011 Sep 1

• Antibiotics are commonly prescribed
  23%, Minnesota (Smith, K, et al, Pediatr Infect Dis J. 2011 Sep 1)
Volume Expand

- Comfort
- Vascular protection in view of HUS risk
- q12 h CBC (drop the hemoglobin)
- daily BUN, creatinine, electrolytes
- K is OK if K is normal or low
- Wait for platelets to rise
  (single determination rarely sufficient)
Non-oligoanuric

Oligoanuric

creatinine

creatinine


What variables are associated with good outcomes?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good outcome</th>
<th>Poor outcome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Day 2</td>
<td>Day 3</td>
<td>0.066</td>
</tr>
<tr>
<td>First culture</td>
<td>Day 2</td>
<td>Day 3</td>
<td>0.02</td>
</tr>
<tr>
<td>First IV started</td>
<td>Day 3 (0-4)</td>
<td>Day 4.5 (2-9)</td>
<td>0.01</td>
</tr>
<tr>
<td>First Cultue obtained</td>
<td>Day 2 (0-4)</td>
<td>Day 3 (2-9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Culture +</td>
<td>Day 4 (2-4)</td>
<td>Day 7 (3-9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pediatrics. 2005;115:e673-80
Fig 2. Volume and characteristics of fluids that were administered during first 4 days of illness

A. Total intravenous fluid volumes (L/m²/first 4 days of illness)

B. Total intravenous sodium (mmol/m²/first 4 days of illness)

C. Total intravenous free water (L/m²/first 4 days of illness)

No Oligoanuria
Oligoanuria

P = .002

P = .001

P = .717
## Logistic Models

### Table 4. Logistic Models

<table>
<thead>
<tr>
<th>Logistic Model</th>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Age</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>2.9 (0.7-11.4)</td>
</tr>
<tr>
<td></td>
<td>Total intravenous fluid given during the first 4 days of illness</td>
<td>6.1 (0.8-46.8)</td>
</tr>
<tr>
<td></td>
<td>Total intravenous sodium given during the first 4 days of illness</td>
<td>1.0 (0.97-1.0)</td>
</tr>
<tr>
<td>Second(^a)</td>
<td>Antibiotics</td>
<td>3.1 (0.8-11.9)</td>
</tr>
<tr>
<td></td>
<td>Total intravenous fluid given during the first 4 days of illness</td>
<td>1.4 (1.0-2.0)</td>
</tr>
<tr>
<td>Final(^b)</td>
<td>Total intravenous sodium given during the first 4 days of illness</td>
<td>1.4 (1.0-1.9)</td>
</tr>
</tbody>
</table>

\(^a\) Variables with P-values of greater than .20 were eliminated from the first model. Also, the colinear variable of sodium given in the first 4 days of illness was taken out because it had less significance than volume given.

\(^b\) Variables with P-values of greater than .05 were eliminated from the model. The final model has only volume given during the first 4 days.

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Detection Acceleration

Every second counts:
  presentation → specimen
  (come in now)
  Specimen → inoculation (swab OK)
  Inoculation → interpretation
  (don’t worry about H7, coli confirmation)
  Report → health department (do it now)
4H Management

- Hospitalize
- Hydrate
- Hold antibiotics
- Health Department