Antibiotic therapy of acute gastroenteritis

Potential goals

- Clinical improvement (vs control)
- Fecal eradication of the pathogen and decrease infectivity
- Prevent complications
Acute gastroenteritis

- Viruses
- Bacteria
- Parasites
- Toxins

2-10% in developed countries
10-30% in developing countries
Antibiotics should be clinically and microbiologically beneficial in bacterial gastroenteritis.
## Efficacy of Antibiotic therapy

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Sometimes</th>
<th>No/Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shigella</td>
<td></td>
<td>Salmonella</td>
<td>EHEC</td>
</tr>
<tr>
<td>EIEC</td>
<td></td>
<td>Campylo</td>
<td>Yersinia</td>
</tr>
<tr>
<td>V. cholera</td>
<td></td>
<td>C. difficile</td>
<td>V. parahae</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPEC</td>
<td>Aeromonas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plesiomonas</td>
<td>EAEC</td>
</tr>
</tbody>
</table>
Dehydration: Assessment and Treatment
Clinical approach

♥ Fluid & electrolyte replacement – essential 1st step in management irrespective of the cause
♥ Etiology is seldom known at presentation
♥ Thorough medical history & epidemiology
Clinical approach: antibiotic therapy

Medical history:
- outbreak
- travel
- AAD
- I/C
- sporadic
Antibiotic therapy for acute GE in children

- Pathogen-based approach
- Clinical approach
- Innovative measures
## Impact of Antibiotic therapy of shigellosis

<table>
<thead>
<tr>
<th>Duration, d</th>
<th>Placebo</th>
<th>Amp</th>
<th>%reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>6.0</td>
<td>3.3</td>
<td>45%</td>
</tr>
<tr>
<td>Fever</td>
<td>2.6</td>
<td>1.3</td>
<td>50%</td>
</tr>
<tr>
<td>Fecal excretion</td>
<td>5.0</td>
<td>2.0</td>
<td>60%</td>
</tr>
</tbody>
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# Antibiotic therapy of shigellosis

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<td>Fever</td>
<td>2.6</td>
<td>1.3</td>
<td>50%</td>
</tr>
<tr>
<td>Fecal eradication</td>
<td>5.0</td>
<td>2.0</td>
<td>60%</td>
</tr>
</tbody>
</table>

Complications: Reduces weight loss and Stx levels (80ng/ml/24h), HUS 0.004

Bennish ML, CID 2006
Antibiotic therapy of shigellosis

- Appropriate antibiotic therapy is efficacious
- Development of resistance to the "Drug of Choice" of each decade
  - 1940s - SULFONAMIDES
  - 1960s - TETRACYCLINES
  - 1980s - AMPICILLIN
  - 1990s - TMP-SMX
ANTIMICROBIAL RESISTANCE OF SHIGELLA IN CENTRAL ISRAEL

<table>
<thead>
<tr>
<th>Location</th>
<th>TMP-SMX</th>
<th>AMP</th>
<th>NAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>67%</td>
<td>91%</td>
<td>0.3</td>
</tr>
<tr>
<td>Israel</td>
<td>90%</td>
<td>81%</td>
<td>0.3</td>
</tr>
<tr>
<td>Brazil</td>
<td>84%</td>
<td>90%</td>
<td>8%</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>80%</td>
<td>73%</td>
<td>51%</td>
</tr>
<tr>
<td>Kenya</td>
<td>100%</td>
<td>98%</td>
<td>83%</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td>13%</td>
</tr>
</tbody>
</table>
Azithromycin vs cefixime in childhood shigellosis

Basualdo et al, PIDJ 4/2005

182 children 6m-5y with dysentery
75 with shigellosis, 80% S. flexneri

<table>
<thead>
<tr>
<th></th>
<th>AZI</th>
<th>CFX</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td>93%</td>
<td>78%</td>
<td>0.1</td>
</tr>
<tr>
<td>Diarrhea days</td>
<td>2.5</td>
<td>3.9</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>In vitro susceptibility</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Bacteriologic cure</td>
<td>93%</td>
<td>59%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

In adults: a single 1 gm dose
Antibiotic therapy of shigellosis

Treatment of choice 2013

❤️ Oral – Azithromycin
10/5 mg/kg/d, 5 days

❤️ Parenteral – Cefriaxone
50 mg/kg/d, 2-5 days

❤️ Alternative – IV/PO Ciprofloxacin
10mg/kg X2/d, 3-5 days
Antibiotic therapy of STEC (EHEC)

Major goal: reduce HUS! (mortality)

>2,500 GE cases (Europe, USA)
>820 HUS (adult females)
>40 deaths

Outbreak of Shiga toxin-producing E. coli in Germany (15 June 2011, 11:00)

The NEW ENGLAND JOURNAL of MEDICINE

Epidemic Profile of Shiga-Toxin–Producing Escherichia coli O104:H4 Outbreak in Germany — Preliminary Report
Antibiotic therapy of E. coli O157:H7

Wong et al, NEJM 2000

- Non-randomized prospective cohort study, E. coli O157:H7
- 47 coop labs, 71 children <10y
- No clinical protocol or treatment guidelines
- HUS: 5/9 (56%) receiving ab
  - 5/62 (8%) no ab
Antibiotic therapy of E. coli O157:H7

- RR 14.3, CI 3-71, p<0.001
- Characteristics of the groups-similar; multivariate analysis
- Conclusions:
  - ab therapy increases the risk of HUS
  - no ab until culture results!
- Similar design and conclusions in a follow-up study (CID 2012;55:33-41)
Induction of phage-mediated toxin production by ciprofloxacin (JID 2004; 181:664).
Antibiotic therapy of E. coli O157:H7

Previous study

Ikeda et al, Clin Nephrol 1999; 52:357

Non-randomized controlled study
292p-36 HUS (12%). fosfomycin <d3: OR 0.09 (0.01-0.79)
Antibiotic therapy of EHEC

- A meta-analysis: no increased risk (JAMA 2002; 288:996).

- “The time has come to move forward: RCT” (CID 2006; 42:1804).
Minnesota surveillance for O157 and HUS

1996-2002: 1417 cases, 76 (5%) developed HUS

Cases of O157-related HUS compared to matched O157-no-HUS controls

Ab treatment collected retrospectively
HUS was associated with more severe illness!!!
Antibiotic therapy and HUS

### TABLE 2. Antibiotic Treatment Frequencies for Antibiotics Used Within 3 Days After the Onset of Diarrhea in *E. coli* O157-infected Hemolytic Uremic Syndrome (HUS) Cases and *E. coli* O157-infected Non-HUS Controls

<table>
<thead>
<tr>
<th>Antibiotic Variable</th>
<th>Cases (n = 63) Number (%)</th>
<th>Controls (n = 125) Number (%)</th>
<th>Matched OR</th>
<th>95% CI</th>
<th>P</th>
<th>Adjusted Matched OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic</td>
<td>19 (30)</td>
<td>25 (20)</td>
<td>1.8</td>
<td>0.9–3.7</td>
<td>0.12</td>
<td>1.5</td>
<td>0.5–4.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Any bactericidal antibiotic†</td>
<td>12 (19)</td>
<td>6 (5)</td>
<td>5.2</td>
<td>1.7–16.4</td>
<td>&lt;0.01</td>
<td>5.1</td>
<td>1.2–21.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Bactericidal antibiotic only</td>
<td>11 (17)</td>
<td>4 (3)</td>
<td>9.8</td>
<td>2.2–44.7</td>
<td>&lt;0.01</td>
<td>12.4</td>
<td>1.4–110.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Any bacteriostatic antibiotic†</td>
<td>8 (13)</td>
<td>21 (17)</td>
<td>0.7</td>
<td>0.3–1.7</td>
<td>0.38</td>
<td>0.3</td>
<td>0.08–1.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Bacteriostatic antibiotic only</td>
<td>7 (11)</td>
<td>19 (15)</td>
<td>0.7</td>
<td>0.3–1.7</td>
<td>0.41</td>
<td>0.3</td>
<td>0.09–1.4</td>
<td>0.14</td>
</tr>
<tr>
<td>β–lactams</td>
<td>9 (14)</td>
<td>1 (1)</td>
<td>17.1</td>
<td>2.2–135.0</td>
<td>&lt;0.01</td>
<td>11.3</td>
<td>1.2–106.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>4 (6)</td>
<td>2 (2)</td>
<td>7.1</td>
<td>0.8–64.4</td>
<td>0.08</td>
<td>4.5</td>
<td>0.4–49.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Quinolones</td>
<td>1 (2)</td>
<td>3 (2)</td>
<td>0.8</td>
<td>0.07–8.9</td>
<td>0.84</td>
<td>1.5</td>
<td>0.06–35.4</td>
<td>0.80</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>1 (2)</td>
<td>2 (2)</td>
<td>0.8</td>
<td>0.07–8.9</td>
<td>0.84</td>
<td>0.8</td>
<td>0.05–12.3</td>
<td>0.86</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>6 (10)</td>
<td>20 (16)</td>
<td>0.5</td>
<td>0.2–1.4</td>
<td>0.21</td>
<td>0.3</td>
<td>0.07–1.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Macrolides</td>
<td>3 (5)</td>
<td>2 (2)</td>
<td>2.6</td>
<td>0.4–16.0</td>
<td>0.29</td>
<td>1.3</td>
<td>0.08–20.1</td>
<td>0.86</td>
</tr>
</tbody>
</table>

### TABLE 3. Antibiotic Treatment Frequencies for Antibiotics Used Within 7 Days After the Onset of Diarrhea in *E. coli* O157-infected Hemolytic Uremic Syndrome (HUS) Cases and *E. coli* O157-infected Non-HUS Controls

<table>
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<tr>
<th>Variable</th>
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<th>Controls (n = 125) Number (%)</th>
<th>Matched OR</th>
<th>95% CI</th>
<th>P</th>
<th>Adjusted Matched OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic</td>
<td>27 (43)</td>
<td>38 (30)</td>
<td>1.7</td>
<td>0.8–3.4</td>
<td>0.1</td>
<td>1.2</td>
<td>0.5–3.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Any bactericidal antibiotic†</td>
<td>17 (27)</td>
<td>10 (8)</td>
<td>5.3</td>
<td>1.9–14.8</td>
<td>0.001</td>
<td>3.5</td>
<td>1.1–11.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Bactericidal antibiotic only</td>
<td>16 (25)</td>
<td>5 (4)</td>
<td>26.6</td>
<td>3.5–202.2</td>
<td>0.002</td>
<td>18.0</td>
<td>1.9–170.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Any bacteriostatic antibiotic†</td>
<td>11 (17)</td>
<td>33 (26)</td>
<td>0.5</td>
<td>0.2–1.1</td>
<td>0.07</td>
<td>0.2</td>
<td>0.05–0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Bacteriostatic antibiotic only</td>
<td>10 (16)</td>
<td>28 (22)</td>
<td>0.5</td>
<td>0.2–1.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.08–1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>β–lactams</td>
<td>14 (22)</td>
<td>5 (4)</td>
<td>6.2</td>
<td>2.0–19.0</td>
<td>0.001</td>
<td>4.3</td>
<td>1.1–17.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>6 (10)</td>
<td>2 (2)</td>
<td>11.1</td>
<td>1.4–92.5</td>
<td>0.03</td>
<td>4.6</td>
<td>0.4–49.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Quinolones</td>
<td>1 (2)</td>
<td>4 (3)</td>
<td>0.5</td>
<td>0.04–5.7</td>
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<td>30 (24)</td>
<td>0.4</td>
<td>0.2–1.0</td>
<td>0.05</td>
<td>0.2</td>
<td>0.04–0.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Macrolides</td>
<td>3 (5)</td>
<td>5 (4)</td>
<td>1.1</td>
<td>0.3–4.6</td>
<td>0.9</td>
<td>0.6</td>
<td>0.07–5.3</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Odds ratios adjusted for self-reported vomiting, fever, blood in stool, and gender.
†Bactericidal antibiotics included those in the following classes: β–lactams, nitroimidazoles, quinolones, and aminoglycosides. Bacteriostatic antibiotics included those in the sulfonamide and macrolide classes.
OR indicates odds ratio; CI, confidence interval.
Antibiotic therapy of EHEC

Controversies

♥ Non-O157:H7 serotypes?
Uncontrolled use of azithromycin during the O104:H4 outbreak in Germany reduced STEC shedding

♥ Empiric therapy?

Antibiotics are not recommended for O157 infections
Thinking outside the box: Stx Monoclonal Abs

Rocha et al, Toxins 9/2012; 4:729-47

- **Rationale:** Inhibit pathogenesis-based toxin activity
- **Mabs** against B subunit of Stx1 (3E2) were prepared
- **Neutralized ~80%** of the activity of Stx1 and Stx2
- **Timing of administration?**
ANTIBIOTIC TREATMENT OF SALMONELLA GE

Cochrane Database Syst Rev

- search for randomized (quasi) trials
- 20 trials - 778p, 258 children
  - ab vs placebo or no ab

- Results - antibiotics: no sig effect on fever, diarrhea
  - < pos cultures during 1st w of t
  - > pos cultures after 3w
  - > adverse effects
ANTIBIOTIC TREATMENT OF SALMONELLA GE

No effect on GE; in high-risk patients

- neonates and young infants (<3m)
- immune deficiency (AIDS, CGD)
- malignancy, especially leukemia, lymphoma
- steroid or immunosuppressive therapy
- asplenia or sickle cell disease
- IBD, gastrectomy
- fever >5d, severe course?

Yang, EJCMID 2004; Clin Microbiol Infect 2012
ANTIBIOTIC TREATMENT OF CAMPYLOBACTER GE

CID 2007; 44:696-700

Meta-analysis of 11 double-blind, placebo-controlled studies

Ab reduced the duration of diarrhea by 1.3d

Effect more pronounced in dysentery and if Ab started <3d of onset

Reduced fecal excretion and infectivity
Cholera

- 2011 global estimate: 2.8 million cases, 100,000 deaths
- Haiti – last 2 years: >600,000 cases, attack rate 6.1%, 7,436 deaths
Cholera in Rwanda
Antibiotic treatment of Cholera


- Antibiotics reduce the duration of Cholera diarrhea by ~50% and the duration of pathogen excretion to ~1 day
- Adjunct to rehydration
- 1st line: azithromycin 20 mg/kg once or doxycycline 2 mg/kg bid
- 2nd line: ciprofloxacin or TMP/SMX (if susceptible)
- Zinc supplementation is recommended
Thinking outside the box: Stool therapy???

- CDI: 15-26% hard-to-treat recurrence
- Persistent spores
- Disturbed microbiota
- RCT in 43 relapsed CDI

**Figure 3.** Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.
Acute sporadic GE

Viral

Cholera

ETEC

Shigella

Salmonella

Campylobacter

EHEC?
Acute sporadic GE

watery

(cholera)

others

No Ab

inflammatory

Shigella

Salmonella

Campylobacter

Consider Ab

inflammatory others

No Ab

inflammatory others

Shigella

Salmonella

Campylobacter

Consider Ab
Bloody/mucous diarrhea

Low or no fever
- EHEC
- Mild Shigella
  - Ab?

High fever
- Shigella!
- Salmonella
  - Campylobacter
  - Ab