Not All Diarrhea Is Created Equally

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Disclosure

I have no relevant financial relationships with the manufacturers of any commercial products and/or provider of commercial services discussed in this CME activity.

I will be discussing an unapproved/investigative use of a commercial product in my presentation.

2-year-old Girl with Bloody Diarrhea

- Previously healthy girl with onset of diarrhea and vomiting on 12/7 and admitted to the hospital on 12/10
- Seemed to have pain starting 12/6
- No fever
2-year-old Girl with Bloody Diarrhea

- On 12/8 had blood streaked stool and went to the ED
- Decreased po intake
- Had contact previous month with infant who subsequently had STEC and HUS
- No significant travel history
- Parents and 4-month old sibling were well

2-year-old Girl with Bloody Diarrhea

- Temp 97.8°, heart rate 131, resp rate 22, O2 saturation 98% on room air
- Ill appearing, not toxic
- Abdomen: non-tender, not distended
- Nurse noted capillary refill to be <2 seconds

Labs in ED

- WBC 22.6, Hgb 12.6, Plt count 308,000
  - 4 bands, 69 sets, 18 lymphs, 9 mono
  - toxic granulation and Burr cells noted
- Sodium 139, Potassium 3.5, Chloride 103, Carbon dioxide 15
  - Anion gap 21
- Creatinine 0.5, BUN 10
ED Management

- Received 20 cc/kg normal saline in ED
- Was given ceftriaxone and stool studies sent for culture, *Clostridium difficile* assay, and ova and parasites
- Ordered abd CT with contrast but not completed as IV infiltrated
- Had grossly bloody stool in the ED so admitted to the PICU

Initial Management

- Got 10 cc/kg of LR
- Had decreased urine output overnight 12/9-12/10
- Hemoglobin decreased to 9.6 on 12/10 and schistocytes noted
Subsequent Course

- Intubated 12/11 for acute respiratory failure
- Seizure activity 12/12 and started keppra
- Four plasmapheresis treatments from 12/11-12/16
- Continuous venovenous hemodiafiltration started on 12/12
  - combination of hemofiltration and hemodialysis
- Transferred to CMH on 12/18

STEC

- Shiga toxin-producing *Escherichia coli*
  - *E. coli* that contain genes encoding one or more Shiga-toxin
    - Stx1 and Stx2
    - Stx1 is closely related to Stx of *Shigella dysenteriae*
  - Enterohemorrhagic *E. coli* (EHEC) are the subset of STEC that cause human disease

STEC Pathogenesis

- Causes a spectrum of disease ranging from asymptomatic carriage (rare) to diarrhea, bloody diarrhea, and hemolytic uremic syndrome (HUS)
- Do not invade the bloodstream
- Clinical manifestations a consequence of toxemia absorbed from the gut
- Toxemia occurs early in illness, is short-lived, and is potentially cleared by the time patients present
STEC Pathogenesis

There is evidence of thrombin generation, increased plasminogen activator inhibitor type 1 activity, intravascular fibrin accretion, and shearing of von Willebrand factor multimers prior to overt renal injury and even in children whose course resolves without severe microangiopathy.

_E. coli O157:H7_

- _E. coli_ O157:H7 is the predominant cause of HUS
- Causes epidemic and sporadic illness
- Sporadic infections are more common
- Most clinical data of EHEC pertains to _E. coli_ O157:H7
- Does not ferment sorbitol unlike most commensal _E. coli_ and almost all non-_E. coli_ O157:H7 EHEC
- Colorless colony on sorbitol MacConkey agar plate

_In an 11-center study (Hickey CA et al, Arch Pediatric Adolesc Med 2011) of 50 children with HUS, 27 were positive for _E. coli_ O157:H7 and 1 was positive for _E. coli_ O121:H19_
- Microbiologic data were negative or incomplete for the other 23
- In a study from Connecticut (Hadler JL et al, Clin Infect Dis 2011) of the 229 patients infected with non-O157:H7 EHEC, only 1 developed HUS
- 45 of the 434 patients infected with _E. coli_ O157:H7 developed HUS
**E. coli O157:H7 Clinical Presentation**

- Incubation period ~3 days
- Usually present with non-bloody diarrhea
- Can have antecedent abdominal pain, vomiting, or transient fever
- ~50% report a history of fever but fever is infrequent in the health care setting
- Diarrhea is almost always painful
- In about 80% of cases diarrhea becomes bloody
- 2-3 days after onset of diarrhea
- Bloody diarrhea generally lasts 3-5 days

**HUS**

- Stringently defined as hemolytic anemia (Hct <30% with smear evidence of hemolysis), thrombocytopenia (<150,000), and renal insufficiency (serum creatinine higher than the upper limit of normal for age)
  - Thrombocytopenia typically occurs first, followed by anemia and then renal insufficiency
- 15-20% of culture proven cases of *E. coli* O157:H7 develop HUS
- Typically manifested 5-13 days after onset of diarrhea

**Oligoanuric HUS**

- Oligoanuric HUS is HUS in which urine output is <0.5 ml/kg/hour for at least 24 consecutive hours
  - Categorically worse than nonoligoanuric HUS
- About two-thirds of children with EHEC-related HUS is oligoanuric and requires dialysis
Risk Factors for *E. coli* O157:H7 HUS

- Under 5 years of age
- Leukocytosis
- Antibiotic exposure
  - In a prospective cohort study of 259 children infected with *E. coli* O157:H7 (Wong CS et al, Clin Infect Dis 2012;55:33-41) antibiotic exposure in the first week of diarrhea when controlling for WBC had aOR = 3.62 (36% vs 12%, risk difference of 24.46%)
  - for oligoanuric HUS 12% vs 3%
- Anti-mobility agents
- History of vomiting (aOR 3.05)

Lab/Imaging Studies at Presentation

- Stool culture or equivalent
- CBC
- Electrolytes, creatinine, BUN
- Ultrasonography may be useful if intussusception is suspected
- CT or contrast studies generally not necessary or helpful

Management of Acute (<1 week) Bloody Diarrhea

- Also applies to a symptomatic patient (abdominal pain, non-bloody diarrhea) known to have contact with someone with proven or suspected STEC
Elements at Presentation that Suggest *E. coli* O157:H7 Infection

- Non-bloody diarrhea that becomes bloody after 1-3 days
- More than 5 stools in past 24 hours
- No fever at presentation to medical care
- Tender abdomen
- Pain is worse with defecation

Early Volume Expansion and Nephroprotection

- Intravenous volume expansion during the first 4 days of *E. coli* O157:H7 related diarrhea was strongly associated with a decreased risk of oligoanuric HUS during subsequent HUS

Initial Empiric and Symptomatic Therapy

- **NO ANTIBIOTICS**
  - multiple studies have shown an increased risk of HUS and no study has shown a benefit from antibiotic treatment
  - antibiotic use also associated with greater risk of oligoanuric HUS
  - Withhold antimotility agents, narcotics, and NSAIDs
  - Infuse ≥20 ml/kg of normal saline
Initial Empiric and Symptomatic Therapy

- Continue IV isotonic crystalloid at maintenance
- Repeated boluses of normal saline if there is any question of diminished urine output, assuming there is no evidence of volume overload
- Peripheral edema should not prompt fluid restriction if there is no central overload
- CBC, electrolytes, creatinine and BUN every 12 hours for the first several days of hospitalization
- Until the platelet count is increasing or there is evidence of therapeutic hemodilution (0.5 g/dl/12 hour)
- Absolute or relative hemoconcentration in early HUS is associated with worse outcomes

Initial Empiric and Symptomatic Therapy

- The platelet count, clinical condition, and the day of illness are the most important indicators of patient status
- Risk of HUS is greatly diminished when the platelet count is rising or stable and symptoms are resolved or resolving

6-year-old girl

- Admitted with diarrhea for one month
- ~6 watery stools per day
- No gross blood
- Daily fever past month
- Normal temp during the day and then fever up to 103°F late night/early am
6-year-old girl

- Had positive *Clostridium difficile* stool assay after having diarrhea for ~2 weeks
- Treated with oral metronidazole for 4 days and switched to oral vancomycin since she was not improved
- Completed 10 days of treatment with vancomycin and not improved
- Decreased appetite

What Now?
WBC 9.4 with 62% sees, 4% bands, 25% lymphs, 2% eos
Hemoglobin 10.0, MCV 72.1 (75 - 87)
Platelet count 407,000, ESR 28
Electrolytes, BUN, creatinine normal

Clostridium difficile PCR assay negative
Stool culture negative

Endoscopy and pathology consistent with Crohn's disease
C. Difficile Diagnostic Tests

Two tests frequently used as “gold standards”

- Cytotoxic stool culture (CC)
  - Able to detect the presence of toxigenic organisms even in small quantities, but it does not categorically identify them as the cause of the diarrhea
  - toxin may be produced in subclinical quantities in vivo
- Cell cytotoxicity assay (CCTA)
  - Identifies free C. difficile toxin in the stool
  - Establishes the association of symptoms to C. difficile more reliably than CC, but it may be negative if concentrations of toxin are low

Three additional assays

- NAAT (PCR or loop-mediated isothermal amplification)
  - Detects the gene encoding C. difficile toxin or the toxin regulatory gene
- Toxin immunoassay (toxin EIA)
  - Essentially equivalent to CCTA
  - Decreased sensitivity
- Glutamate dehydrogenase (GDH) assay
  - Expressed uniformly in high quantities by C. difficile but does not differentiate toxigenic from nontoxigenic strains

Detect presence of the organism

- CC, NAAT, GDH

Detect presence of the toxin

- CCTA, toxin EIA
**Clostridium Difficile Testing**

- Should only be performed in children with diarrhea and prioritized to those with known risk factors for C. difficile infection.
- Most appropriate in children older than 2 years.
- If <2 years testing should only be pursued if symptoms persist in the absence of alternative diagnoses or if the clinical presentation is severe or CDI-consistent.
- For otherwise healthy children with diarrhea in the community and no known exposures or risk factors for CDI, C. difficile testing is rarely indicated, particularly if diarrhea is mild.

Sammon JS and Toltzis P. *Infect Dis Clin N Am* 2015

**Treatment**

- **IDSA guideline 2010**
  - vancomycin for severe disease
  - metronidazole for mild-to-moderate disease for initial episode and first recurrence
  - vancomycin for subsequent recurrences
- **Recent Review**

Pediatric dose for fidaxomicin is 32 mg/kg/day.

Key Points

- Two recent, randomized, controlled studies have helped define the role of vancomycin and fidaxomicin in the treatment of CDI.
- The first study confirmed higher cure rates using vancomycin over metronidazole for patients with initial or recurrent CDI.
- The second study confirmed superior sustained response (no recurrence within one month) for fidaxomicin over vancomycin for patients with an initial or first CDI recurrence.
- In patients with multiple recurrent CDI, nonstandard antibiotic treatments, such as taper and pulse strategy, using vancomycin and potentially fidaxomicin may be effective.

Fecal Microbiota Transplantation (FMT)

- Disruption of the gut microbiome is a prerequisite for CDI and can persist after treatment.
- FMT is highly effective in treating recurrent CDI.
  - overall 92% of patients had resolution of their recurrent CDI after one or more treatments
  - after only one treatment 89% had resolution of symptoms.

Safety of FMT

- There have been no serious adverse effects directly attributable to FMT.
- symptoms of an irritable bowel (constipation, diarrhea, cramping, bloating) have been reported shortly after FMT and were usually transient (<48 hours).
- No cases of septicemia reported.
- Long term safety yet to be established.
Probiotics for Prevention of C. Difficile Diarrhea (CDD)

- IDSA guideline from 2010 did not recommend probiotics due to limited data and potential for bloodstream infection
  - pooled findings of 23 randomized controlled trials of 4213 children and adults that evaluated many different probiotics
  - overall, probiotics were found to significantly reduce the frequency of CDD (RR 0.36 with 95% CI 0.26-0.49)

Probiotics for Prevention of C. Difficile Diarrhea (CDD)

- Similar effects of the probiotics were observed when studies for children and adults were compared
- Efficacy remained statistically significant for the yeast Saccharomyces boulardii and a blend of Lactobacillus acidophilus and Lactobacillus casei

Probiotics for Prevention of C. Difficile Diarrhea (CDD)

- Caution is needed in interpreting the findings of the meta-analysis since only 3 of the included trials reported a statistically significant effect and research methods and reporting were assessed to be poor in many of the studies included in the review
- A recent large randomized placebo controlled study in adults (≥ 65 years) did not demonstrate a statistically significant effect
Questions?