15 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Gastrointestinal Disease: Etiologic Agents

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

OBJECTIVES

- List the most communicable and most lethal enteric pathogens
- Provide a review of the new developments for enteric pathogens including Shigatoxin-producing *E. coli* and travelers' diarrhea treatment
- Indicate differences between the seafood neurotoxin disorders
- Critique PCR methods to establish enteric infection diagnosis

ANNUAL DEATHS FROM ENTERIC PATHOGENS IN U.S.

- 83% of deaths occur in adults ≥ 65 years of age; Pediatric deaths from diarrhea 369/year
- *C. difficile* infection (CDI) (29,000) is the most common cause of death (>70% of total)
- Noroviruses (797/year) often in elderly in hospitals or nursing homes
- *Salmonella* (378) and
- *Listeria* (260)

Hall, AJ et al. Clin Infect Dis 2011;55:216-23
CDC http://www.cdc.gov/foodborneburden/2011-foodborne-estimates.html

PATHOGEN COMMUNICABILITY
ALL INFECTIOUS DISEASES SHOW A DOSE THRESHOLD FOR ILLNESS

Pathogen Group	Expected Inoculum Size
Highest rate of transmissibility*: *Shigella*, Noroviruses	10 to 100 organisms
High rate of transmissibility: *Giardia*, *Cryptosporidium*, *Salmonella* (infants only)	80-500 organisms
Lower communicability: Shiga toxin-producing *E. coli*, *Salmonella* (older children/adults), *Campylobacter*	500 to 100,000 organisms
Absence of communicability: enteroinvasive and enterotoxigenic *E. coli* (EIEC, ETEC) and *Vibrio cholerae*	100,000 to > 1,000,000 organisms

*low inoculum requirement, stability in environment, reservoir in children

Immunocompromised/elderly people, infants, those on proton pump inhibitors may be susceptible to lower inoculum sizes

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 PREVIEW QUESTION

QUESTION #1

Low Dose Pathogens Commonly Cause Diarrhea Outbreaks in Day Care Center Which of the following doesn't fit?

A. *Shigella*
B. *Cryptosporidium*
C. *Giardia*
D. *Campylobacter jejuni*
E. Norovirus

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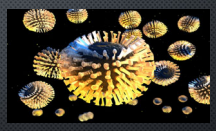
VIRAL GASTROENTERITIS

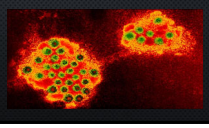
ROTAVIRUS

- KILLER OF 129,000 INFANTS GLOBALLY WITH DECREASES AS VACCINES ARE MADE AVAILABLE
- DECREASED RATES WORLDWIDE THANKS TO INEXPENSIVE VACCINES



NOROVIRUSES (NOW THE MOST COMMON CAUSE OF ENTERIC INFECTION WORLDWIDE)

- 200,000 ANNUAL DEATHS IN THE DEVELOPING WORLD WITH YOUNG CHILDREN AND THE ELDERLY MOST SUSCEPTIBLE
- > 20 MILLION CASES FOODBORNE DISEASE IN U.S. (HALF OF ALL CASES); 26% OF CASES PRESENTING TO ED
- 20% OF U.S. POPULATION NOT SUSCEPTIBLE RELATED TO ANTIGENS THAT DETERMINE BLOOD TYPES
- MAJOR PATHOGEN GENO GROUP II GENOTYPE 4 (GII.4) WITH GII.17 STRAINS CURRENTLY EMERGING
- SECONDARY ATTACK COMMON (17%)
- MOST COMMON SETTING FOR OUTBREAKS HEALTHCARE FACILITIES, AND NURSING HOMES



SHIGA TOXIN-PRODUCING *E. COLI* INFECTION (~300,000 CASES IN U.S.)

***E. coli* O157**

SORBITOL-NON-FERMENTING

SORBITOL-MACCONKEY AGAR & O157 SEROTYPING

E. coli* non-O157

Sorbitol-positive, test stools, broth or culture plate for *Stx* 1 and 2 by EIA and if positive send *E. coli* to Health Lab

Common groups in U.S. O26, O111, O103, O45, O145 and O121

Hemorrhagic colitis

Dysentery

85%

13%

Hemolytic Uremic Syndrome

9%

9%

STEC strains are threatening our food supply

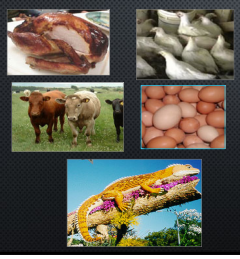
Person-to-person spread seen in day care centers and in families

SHIGA TOXIN PRODUCTION UNDER PHAGE CONTROL

- SOME ANTIBIOTICS MOBILIZE PHAGE (E.G. FLOUROQUINOLONES, TMP-SMX),

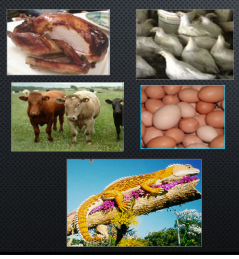
  AZITHROMYCIN AND RIFAXIMIN DO NOT
- ANTIBIOTICS ARE NOT INDICATED IN THIS INFECTION BUT STAY TUNED
- HUS CAN BEGIN AS SYMPTOMS RESOLVE USUALLY WITHIN 3 WEEKS OF INFECTION. ~15% OF CHILDREN DEVELOP, LESS IN ADULTS WITH INCREASING RATE IN ELDERLY. DEATH RATE 3-5%
- WHILE COMPLEMENT IS INVOLVED IN TYPICAL HUS, ANTI-COMPLEMENT MONOCLONAL ANTIBODIES (ECULIZUMAB AND RAVULIZUMAB) ARE APPROVED ONLY FOR ATYPICAL HUS
- TREATMENT IS SUPPORTIVE: DIALYSIS, ACE INHIBITORS, ARBS FOR CONTROL OF HYPERTENSION AND ANTI-SEIZURE DRUGS

NON-TYPHOID SALMONELLOSIS



- ANTIBIOTICS ARE NOT HELPFUL IN NON-BACTEREMIC FORMS BUT ARE LIFE SAVING IN BACTEREMIA
- BECAUSE OF DEEPER MUCOSAL PENETRATION BACTEREMIA RATE IN HEALTHY OCCURS IN 8% OF HEALTHY PEOPLE IN U.S., HIGH-RISK GROUPS: ELDERLY, INFANTS 1-3 MONTHS, SS DISEASE, INFLAMMATORY BOWEL DISEASE, IMMUNOCOMPETENCE OR ON STEROIDS) RATE UP TO 50%

NON-TYPHOID SALMONELLOSIS



- THE HIGHEST FREQUENCY OF INFECTION IS IN INFANTS. INFANTS WITH MILK-FILLED STOMACHS CAN BE INFECTED BY LOW INOCULUM SIZE DURING HOUSEHOLD CROSS-CONTAMINATION
- IN A STUDY OF 8,770 PATIENTS WITH INVASIVE DISEASE (POSITIVE BLOOD OR BONE MARROW CULTURE) MORTALITY RATE VARIED BY REGION: AFRICA 17%, ASIA 14%, EUROPE AND USA 10%[1]
- RECENT OUTBREAKS HAVE BEEN TRACED TO PEANUT BUTTER (*S* SENFTENBERG) AND CHOCOLATE PRODUCED IN BELGIUM (MONOPHASIC AND NONMOTILE STRAIN OF *S* TYPHIMURIUM)

1 Marchello CS et al. Lancet Infect Dis 2022;22:692-705

PROTOZOAL PATHOGENS CAUSE PROTRACTED DIARRHEA

- PERSISTENT DIARRHEA (≥ 14 DAYS)
- DIAGNOSTIC CHALLENGES

NEGATIVE TEST GIARDIA, EIA/PCR FOR *E. HISTOLYTICA*, ACID FAST STAINING NOT ROUTINE, MULTIPLEX PCR SOLVES

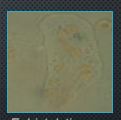
- SPORULATION REQUIRED FOR *CYCLOSPORA* FOR INFECTIVITY
- *CRYPTOSPORIDIUM*

OFTEN HAS AN ANIMALS RESERVOIR, WATER VEHICLE OF TRANSMISSION

- *E. HISTOLYTICA* PRODUCES LIVER ABSCESS MOST IMPORTANTLY IN MALES

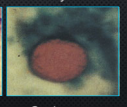
SEROLOGY HELPFUL IN HEPATIC ABSCESS AS STOOLS OFTEN NEGATIVE

Giardia



E. histolytica

Cryptosporidium



Cyclospora

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SEAFOOD FOODBORNE DISEASES

Dinoflagellates (DF) in water are the Source of toxin

Neurotoxigenic Illnesses:

- **Paralytic Shellfish:** toxin from different DF concentrated in in mollusks producing numbness and tingling after 30-60 minutes; serious cases may need respiratory support
- **Ciguatera:** toxin from DF (*Gambierdiscus toxicus*) growing around coral reefs 35°N and 35°S latitudes, that are ingested by large reef fish ~50,000 each year in world, many in travelers, GI symptoms, cold hot reversal and numbness & paresthesias
- **Neurotoxin Inhalation or Shellfish poisoning:** toxin from DF *Karenia brevis* inhaled during algal blooms, biggest problem in asthmatics or the toxin is ingested with mild form of paralytic shellfish poisoning
- **Pufferfish:** toxin from DF in pufferfish (Japanese delicacy)

SEAFOOD FOODBORNE DISEASES

Toxin concentrates in fish or mollusks (histamine-like substances from spoiled fish)

Chemical Illness:

- **Scrombroid** (histamine-like histidine) from improperly refrigerated or preserved tuna, mackerel, mahi-mahi, sardine, anchovy, herring, bluefish, amberjack and marlin causing a histamine reaction: flushing (like sunburn), headache, palpitations, itching, diarrhea within 10-60 minutes with resolution in 12 hours
- People report a peppery, sharp and salty taste
- Heat stable histamine

WHAT'S NEW TRAVELERS' DIARRHEA

ESBL or MDR Enterobacteriaceae Risk Factors:

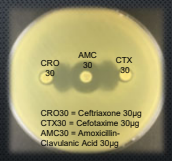
- Travel to tropical and semitropical areas, especially Asia (highest for travel to India)
- Diarrhea increases rate and receipt of antibiotics further increases risk

Endogenous Infections* or Spread to Family Duration of Colonization After Returning Home

- < 3 months to 12 months
- Shorter than when acquired in a hospital

•Treat with antibiobics only moderate to severe Travelers' diarrhea

Extended spectrum beta lactamase-producing Enterobacteriaceae



CRO30 = Ceftriaxone 30µg
CTX30 = Cefotaxime 30µg
AMC30 = Amoxicillin-Clavulanic Acid 30µg

Jiang Z-D, DuPont HL

DIAGNOSTIC APPROACHES IN INFECTIOUS DISEASES MOVING TO PCR

Verigene Luminex Biofire

Biocode

Requires clinical judgement & correlation

- Syndromic approach detects organisms that clinicians may have not thought about/ordered or are difficult to isolate in the lab
- Rapid diagnosis may allow earlier initiation of therapy
- For larger centers, is cost effective
- Has potential to re-define epidemiology and treatment
- In positives, culture of stool yields pathogen in <60%
- Colonizing *C. difficile* in patients associated with false (+), require confirmation with second step
- Interpretation for some pathogens is difficult (e.g. enteropathogenic *E. coli* (EPEC) & enteroaggregative *E. coli* (EAEC)

2017 INFECTIOUS DIARRHEA GUIDELINES (HIGHLIGHTS)

- Exercise clinical judgment when interpreting PCR-based results
- Perform reflex cultures when an organism is identified by PCR for epidemiology and susceptibility testing
- Fecal leukocyte, lactoferrin, calprotectin are not routinely indicated
- Diagnostic testing is not indicated for travelers' diarrhea unless diarrhea persists >14 days, consider *C. difficile* if antibiotic exposure. TD can trigger inflammatory bowel disease or irritable bowel syndrome
- Monitor Cr/Hb in patients with STEC identified in stools at risk for HUS, examine peripheral smear for schistocytes
- Perform endoscopy for persistent, unexplained diarrhea

Shane, et. al. CID 2017:65 e45-80

ORGANISM-SPECIFIC THERAPY

- Shigellosis – Fluoroquinolone or azithromycin
- Non-typhoid salmonellosis – only with sepsis - fluoroquinolone or 3rd generation cephalosporin
- Campylobacteriosis – Azithromycin or erythromycin
- STEC diarrhea – none
- Non-cholera *Vibrio* diarrhea – as shigellosis
- Cholera – doxycyline
- Viral gastroenteritis – ORT, ? Bismuth subsalicylate
- Giardiasis – Tinidazole or nitazoxanide
- Cryptosporidiosis - nitazoxanide
- Cyclosporiasis or Cystoisosporiasis – TMP/SMX
- Enterocytozoon diarrhea – Albendazole
- Intestinal amoebiasis – metronidazole plus diloxanide furoate or paromomycin

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