

44 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD



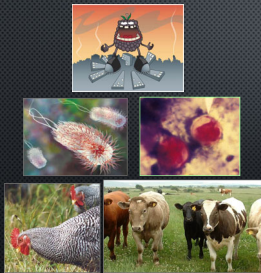
Gastrointestinal Disease: Causative Agents

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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 TRAVELERS' DIARRHEA TREATMENT
- INDICATE DIFFERENCES BETWEEN THE SEAFOOD NEUROTOXIN DISORDERS
- CRITIQUE PCR METHODS TO ESTABLISH ENTERIC INFECTION DIAGNOSIS

THE IMPORTANCE OF DIARRHEA IN THE UNITED STATES

- PREVALENCE 3-7% FOR ADULTS AND 8% FOR CHILDREN ≤ 5 YEARS OF AGE
- 0.6 CASES/PERSON/YEAR
- 48 MILLION CASES OF FOODBORNE DISEASE (HALF DUE TO NOROVIRUSES)



DEATH FROM DIARRHEA IN U.S.

- 11,255 deaths/year: 83% of deaths occur in adults ≥ 65 years of age; Pediatric deaths 369/year
- *C. difficile* infection (CDI) the most common cause of death 7,903* year (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;55:214-23
CDC <http://www.cdc.gov/foodborneburden/2011-foodborne-estimates.html>

*CDC data 29,000 deaths annually

PATHOGEN COMMUNICABILITY ALL INFECTIOUS DISEASES SHOW A DOSE THRESHOLD FOR ILLNESS

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

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QUESTION #1

PREVIEW QUESTION



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

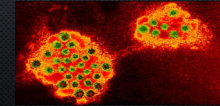
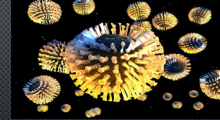
VIRAL GASTROENTERITIS

ROTAVIRUS

- KILLER OF 215,000 INFANTS GLOBALLY
- DECREASED RATES WORLDWIDE THANKS TO INEXPENSIVE VACCINES

NOROVIRUSES

- SAME MORTALITY ESTIMATES AS ROTAVIRUS FOR DEVELOPING WORLD
- > 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)
- SECONDARY ATTACK COMMON (17%)
- INCREASING IN CHILDREN AS ROTAVIRUS DECREASING



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



Hemorrhagic
colitis

Dysentery



85%
13%

Hemolytic Uremic Syndrome

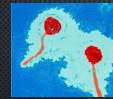


9%
9%

STEC strains are threatening our food supply



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
- IV ECUZUMAB, A MONOCLONAL ANTIBODY CAN IMPROVE RENAL INSUFFICIENCY

QUESTION # 2

WHAT OF THE FOLLOWING IS TRUE ABOUT ECUZUMAB TREATMENT OF HUS?

- A. ECUZUMAB IS NOT APPROVED FOR OTHER INDICATIONS
- B. TREATED PATIENTS ARE SUSCEPTIBLE TO MENINGOCOCCAL INFECTIONS
- C. RED CELL DESTRUCTION IS NOT PREVENTED
- D. COST OF THE DRUG HAS DECREASED WITH INCREASED USE
- E. TREATMENT DOES NOT DECREASE NEED FOR BLOOD TRANSFUSIONS



NON-TYPHOID SALMONELLOSIS



- HIGHEST RATE <1 YEAR AGE
- ANTIBIOTICS ARE NOT HELPFUL IN NON-BACTEREMIC FORMS
- BECAUSE OF DEEP MUCOSAL PENETRATION BACTEREMIA RATE IN HEALTHY OCCURS IN 8% OF HEALTHY PEOPLE, HIGH-RISK GROUPS: ELDERLY, INFANTS 1-3 MONTHS, SS DISEASE, INFLAMMATORY BOWEL DISEASE, IMMUNOCOMPETENCE OR ON STEROIDS) RATE UP TO 50%

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NON-TYPHOID SALMONELLOSIS



- CURRENT EPIDEMIC OF BACTEREMIC DISEASE ALL AGE GROUPS IN SUB SAHARAN AFRICA WHICH RELATES TO HOST & MICROBIAL FACTORS: CO-EXISTENT MALARIA AND HIV INFECTION
- ISRAELI STUDY SHOWING THAT STRAINS SHOWING PERSISTENT INFECTION SHOW CHANGES IN COMPOSITION OF MOBILE GENETIC ELEMENTS (PLASMIDS AND PHAGES) AND AMINO ACID SUBSTITUTIONS CHANGING SNPs ALTERING VIRULENCE AND SECONDARY TRANSMISSION

Marzel, A et al. Clin Infect Dis 2016;62:879-86

PROTOZOAL PATHOGENS CAUSE PROTRACTED DIARRHEA

- PERSISTENT DIARRHEA (≥ 14 DAYS)
- DIAGNOSTIC CHALLENGES
NEGATIVE TEST GIARDIA ELAVPCR FOR E. HISTOLYTICA, ACID FAST STAINING NOT ROUTINE, MULTIPLEX PCR SOLVES
- SPORULATION REQUIRED FOR CYCLOSPORA FOR INFECTIVITY
- CRYPTOSPORIDIUM
ANIMALS RESERVOIR, WATER VEHICLE OF TRANSMISSION
- E. HISTOLYTICA PRODUCES LIVER ABSCESS MOST IMPORTANTLY IN MALES



Serology helpful in hepatic abscess as stools often negative

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

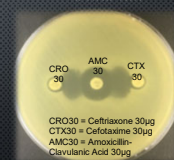
ESBL or MDR Enterobacteriaceae Risk Factors:

- 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 only more severe Travelers' diarrhea

Extended spectrum beta lactamase-producing Enterobacteriaceae



Jiang Z-D, DuPont HL

DIAGNOSTIC APPROACHES IN INFECTIOUS DISEASES MOVING TO PCR



The Positives

- 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

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CHALLENGES MULTIPLEX PCR DIAGNOSIS

The Negatives

- PATHOGENS ARE NOT ISOLATED FOR SUSCEPTIBILITY TESTING AND EPIDEMIOLOGY PURPOSES
- 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)
- EXPENSIVE FOR SMALLER HOSPITALS



Requires clinical judgement & correlation

CHALLENGES MULTIPLEX PCR DIAGNOSIS

MULTIPLEX PCR PLATFORMS: BIOFIRE (22 PATHOGENS), LUMINEX (19 PATHOGENS), BIOCODE (17 PATHOGENS)

TWO REASONS NOT APPROPRIATE FOR ROUTINE STUDY OF DIARRHEA: TOO EXPENSIVE AND LOW CLINICAL YIELD (IDENTIFICATION OF TREATABLE PATHOGENS*)

QUANTITATIVE (qPCR OR TaqMAN ARRAY CARD) CAN DETERMINE INFECTION FROM COLONIZATION BUT AT GREAT COST



*Clark SD et al. Open Forum Infect Dis 2019;6(4).doi:10.1093/ofid/ofz162

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 Cx/Hb IN PATIENTS WITH STEC IDENTIFIED IN STOOLS AT RISK FOR HUS, EXAMINE PERIPHERAL SMEAR FOR SCHISTOCYTES
- PERFORM ENDOSCOPY FOR PERSISTENT, UNEXPLAINED DIARRHEA. EVALUATE HIV AND LYMPHOPENIC PATIENTS FOR CMV AND MAC

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 – doxycycline
- Viral gastroenteritis – ORT, \pm Bismuth subsalicylate
- Giardiasis – Tinidazole or nitazoxanide
- Cryptosporidiosis - nitazoxanide
- Cyclosporiasis or Cystoisosporiasis – TMP/SMX
- Enterocytozoon diarrhea – Albendazole
- Intestinal amoebiasis – metronidazole plus diloxanide furoate or paromomycin

CONCLUSIONS

- INFECTIOUS DOSE INFLUENCES ATTACK RATE AND INCUBATION PERIOD
- NOROVIRUSES • MOST COMMUNICABLE PATHOGEN, CAUSES HALF OF THE CASES OF FOODBORNE DISEASE, REPLACING ROTAVIRUS AS THE MAJOR PEDIATRIC ENTEROPATHOGEN
- IT IS IMPORTANT TO UNDERSTAND STEC AS A PATHOGEN, PATHOGENESIS AND DIAGNOSIS
- NON-TYPHOID SALMONELLA IS CAUSING EPIDEMIC BACTEREMIA IN ALL AGE GROUPS IN SUB SAHARAN AFRICA DUE TO HOST AND MICROBIAL FACTORS
- ANTIBIOTICS TAKEN WHILE IN A DEVELOPING REGION WILL ENCOURAGE COLONIZATION OF ESK COLIFORMS
- MULTIPLEX PCR DIAGNOSTICS HAVE THE POTENTIAL TO REVOLUTIONIZE DIAGNOSIS AND EPIDEMIOLOGY OF INFECTIOUS DIARRHEA

