

MID Transcript – Infectious Diarrheas (Gastroenteritis)
Lecturer: Ada Huang, MD

Everything the speaker said and everything on her slides were directly from the syllabus entry. She said that Murray, pp 424–425, listed some relevant organisms and that individual chapters in that book could be referenced per organism. She also gave two references:

Science 2004 – 304: 242–248 – for molecular/cellular mechanisms of microbial pathogenesis

NEJM 2004 – 350: 38–47 – for a clinical review

What follows is last year’s transcript, also adding nothing to the syllabus entry.

–Anand (apd2104)

Transcriber: Sara Auld

Note: The lecture was given almost verbatim from the syllabus. I have tried to distill down the major points but I would definitely read the syllabus entry pretty carefully.

First off, Table 1 on page 2 of the syllabus entry is KEY to this topic.

Learn this table.

Diarrhea is bad, really bad. It is one of the greatest causes of morbidity and mortality in the world and is particularly bad in developing countries. The syllabus lists examples of recent outbreaks of infectious diarrheas – most of these are related to some sort of food poisoning. These outbreaks tend to get a lot of publicity but most infections are in fact sporadic and isolated. Factors that increase your risk for diarrhea include travel, food-borne outbreaks and institutional settings.

EPIDEMIOLOGY

Infants are at higher risk. They are dependent on others for food and they play with feces and urine. Their risk as infants goes down with breast-feeding (decreased exposure to contaminated food sources and maternal antibodies) but they will then have an increase in risk with weaning.

Living in a developing country increases your risk. You are more likely to live in a crowded place with poor sanitation.

Tropical climates are more likely to have diarrheas from diarrheal-producing toxins such as *E. coli* and parasites. These outbreaks will happen mostly in summer.

Temperate climates are more likely to have diarrheas from viral causes. These outbreaks will happen mostly in winter.

HOST FACTORS/DEFENSE MECHANISMS

Almost all GI pathogens are acquired by the fecal–oral route or by ingestion of contaminated material. The **infectious inoculum** is basically the “dose” of an organism necessary to cause a disease. For most organisms, ingestion of a large number (10^5 – 10^8) of organisms is required to produce disease. These organisms generally require growth in food or water and are not directly transmitted from person to person (unless someone is immunocompromised). *Shigella* (10–100 organisms), shiga–toxin producing *E. Coli* (*E.coli* O157:H7), rotavirus, and parasites (*Giardia/Entamoeba*) require only small numbers to produce disease – they can be directly transmitted from person to person.

Gastric acidity and motility protect you. Anything (i.e. medications) affecting either of these factors can increase your susceptibility. **Normal flora**, mostly anaerobes but some aerobes, protect you by competing with disease causing bugs for attachment sites and nutrients. They also produce substances toxic for pathogens and induce low–level immunity (via. cross–reactivity with pathogens). Antibiotics will decrease your normal flora and thereby increase your risk for GI infections.

The **Goblet cells** of your GI tract produce **mucous**. This mucous has polysaccharides and proteins that trap bacteria, CHO residues that competitively bind bacteria and enzymes that are harmful to bacteria. **Paneth cells** produce peptides that are toxic to bacteria.

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GALT is your basic lymphoid tissue in the gut. Its **M-cells** are phagocytic cells that ingest bacteria and transport them to underlying macrophages as part of a mechanism to produce localized antibodies specific to bacterial pathogens. (Sometimes though, i.e. with *Shigella* and *Salmonella*, the M–cells can provide a portal of entry.) The **IgA** that is produced is secreted across the mucosal cells. It is resistant to degradation by GI proteases and binds bacteria to prevent it from adhering to the GI walls. The IgA also mediates opsonization of organisms. The immune cells induced in the GALT can migrate to other mucosal tissues and produce IgA – this is what happens with breast milk.

MICROBIAL VIRULENCE FACTORS

Most GI bacterial pathogens are gram–negative aerobic bacilli that are members of the **Enterobacteriaceae** family; these organisms share homology at the DNA level.

Adherence is the initial requirement for causing infection or disease; the ability of an organism to adhere correlates with its pathogenicity.

Invasiveness of an organism can cause systemic illness that isn't limited to the GI tract.

There are three main classes of toxins. **Enterotoxins** (*Vibrio cholerae*, enterotoxigenic *E. coli*/EPEC) disrupt the absorptive and secretory functions of intestinal mucosal cells. They do not cause any cell or tissue damage. **Cytotoxins** (*Shigella*, shiga toxin producing *E. coli*/STEC, *Clostridium difficile*, *Entamoeba histolytica*) destroy or kill intestinal mucosal cells and induce an inflammatory response that can cause a visible ulceration. **Neurotoxins** (not a focus of this lecture) (*Staph aureus*, *Bacillus cereus*, *Clostridium botulinum*) act on the ANS to induce changes in GI motility.

ENTEROTOXIN MEDIATED SECRETORY DIARRHEAS

Vibrio Cholerae: Humans are the only known reservoir. The organism is acquired via ingestion of infected food or water. The genome is made up of two circular chromosomes: a larger one that contains most of the virulence factors and a smaller one with “essential genes” for metabolism, signaling and DNA repair. Its adherence is enhanced through **flagellar motility** and **pili**. It also has accessory colonization proteins. **Cholera toxin** is discussed in detail in the syllabus – she only mentioned it in class. It is required for virulence and works by ADP ribosylation of host cell G proteins to increase Na and Cl (and thereby water) transport out of GI mucosal cells and into the gut lumen...giving you diarrhea.

Enterotoxigenic E. coli (EPEC): This organism is the major cause of traveler’s diarrhea and diarrhea in kids in developing countries. Most *E. coli* strains are not pathogenic – but this one has extra virulence factors and does cause disease. It produces two major toxins: **heat labile toxin (LT)** is similar to cholera toxin and interferes with ion and water secretion; **heat stable toxin (ST)** works through a different mechanism with guanylate cyclase to cause ion and water net secretion.

There are no systemic findings or fever with these organisms and they primarily involve the small bowel. They cause profuse watery diarrhea (cholera = “rice water stool”) without fecal leukocytes. There is no cell or tissue destruction.

INFLAMMATORY OR CYTOTOXIN MEDIATED DIARRHEAS

Shigella: This organism causes dysentery, a relatively small-volume diarrhea containing blood and mucous. Humans are the primary reservoir for this highly infectious organism that

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can be transmitted directly from person to person. *Shigella* invades the colonic mucosa through the M-cells and manages to sneak into neighboring mucosal cells before it can be uptaken by macrophages. It invades cells by using **invasion plasmid antigens (Ipa)** – these are cell surface and excreted proteins that induce rearrangement in the host cell cytoskeleton. Then the bacteria can be engulfed by normally non-phagocytic cells and undergo intracellular replication. Then it kills the host cell and is ready to spread to other cells. It uses **IcsA (intracellular spread A)** and **IcsB proteins** to spread into neighboring cells without ever passing through the extracellular environment. This direct cell-to-cell spread allows *Shigella* to evade the

immune system.

Shiga toxin producing E. coli (STEC): This category of organisms includes E. Coli O157:H7 – this organism is not as common as other GI pathogens but is associated with higher morbidity and mortality. It is associated with ground beef food poisoning outbreaks. **Shiga-like toxin** interferes with host cell protein synthesis and causes cell damage and then death; it may target blood vessels. Clinical complications include: hemolytic anemia, thrombocytopenia and acute renal failure.

Clostridium difficile: This is a gram-positive bacillus (vs. the other two just mentioned that are gram-negative) and is seen in association with any antibiotic use. It produces **Toxin A**, **Toxin B** and causes **spore formation**. These spores are not metabolically active and thereby are resistant to antibiotics; retreatment of these infections is often necessary.

The clinical syndrome includes dysentery, fever, abdominal pain, and leukocytosis. Mucosal destruction and inflammation will result in leukocytes and RBCs in the stool. Tests for the specific toxins can be performed with enzyme immunoassays. The colon and large bowel are involved and can exhibit visible erosions and ulcerations.

GI INFECTIONS CAUSING SYSTEMIC ILLNESS

Salmonella: Salmonella causes typhoid fever and food-borne gastroenteritis (especially via. poultry and eggs). There are two major subtypes of salmonella: **Typhi** – humans are the only known reservoir and it causes serious systemic disease i.e. typhoid fever and **non-Typhi** – animals are a major reservoir for these ubiquitous organisms that can cause self-limited GI tract disease (unless a patient is immunocompromised). Salmonella is directly taken up by M-cells or invades GI mucosal cells. It prevents phagosome-lysosome fusion in immune cells and disseminates in the blood. It replicates in the liver and spleen and can then be excreted into the bile and cause a secondary bacteremia and a repeat hematogenous dissemination. It can replicate intracellularly in nonphagocytic cells.

Diarrhea is often not a very prominent clinical symptom. Lab results will show anemia, a decreased WBC count and elevated liver function tests. Blood cultures will be positive in the first week, stool cultures will be positive in the second week.

VIRAL CAUSES OF GASTROENTERITIS

Viral causes constitute 40% of infectious diarrheas in the US. Much less is known about viral diarrhea. They can cause histological changes in the small bowel. They are not associated with any known toxin production but cause functional changes in electrolyte and fluid secretion and CHO absorption. (Several of these viruses are covered in the syllabus but were not discussed in lecture.)

DIAGNOSIS

History: risk factors – infants, Rotavirus; travelers, ETEC; antibiotic use, C. difficile

presence or absence of systemic symptoms (i.e. secretory vs. inflammatory)

character of stool

Physical Exam: fever, presence and degree of volume depletion

Direct Stool Exam: gross description, presence of fecal WBCs, parasite exam, immunoassays

Stool Culture: limited use for E. coli since it is a normal flora but will identify organisms that are generally pathogenic when present (Vibrio cholerae, Shigella, Salmonella, Campylobacter)

Blood Culture: systemic infections, i.e. Salmonella

TREATMENT

Fluid and electrolyte replacement since most infections are self-limited.

Antibiotic therapy is somewhat controversial.

PREVENTION

Pretty common sense stuff for the most part. There is now an oral vaccine available for Salmonella.