Infectious Diarrheal Diseases

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Università
degli Studi
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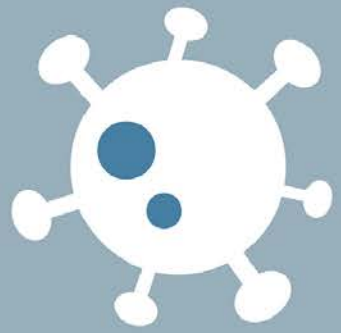


Objectives

- Identify the most common causes of infectious diarrhea in adult patients in resource-rich settings
- Describe how the patient history and clinical presentation of diarrhea may favour viral versus bacterial causes, and which situations benefit from antibiotic therapy
- Recognize warning signs for severe diarrheal disease that require immediate hospitalization and/or antibiotic therapy
- Describe management approach and treatment of common infectious diarrheal pathogens
- We will not be discussing (specifically) diarrheal diseases in resource-poor countries. Information on the special issues managing these infections should be obtained from the WHO guidelines

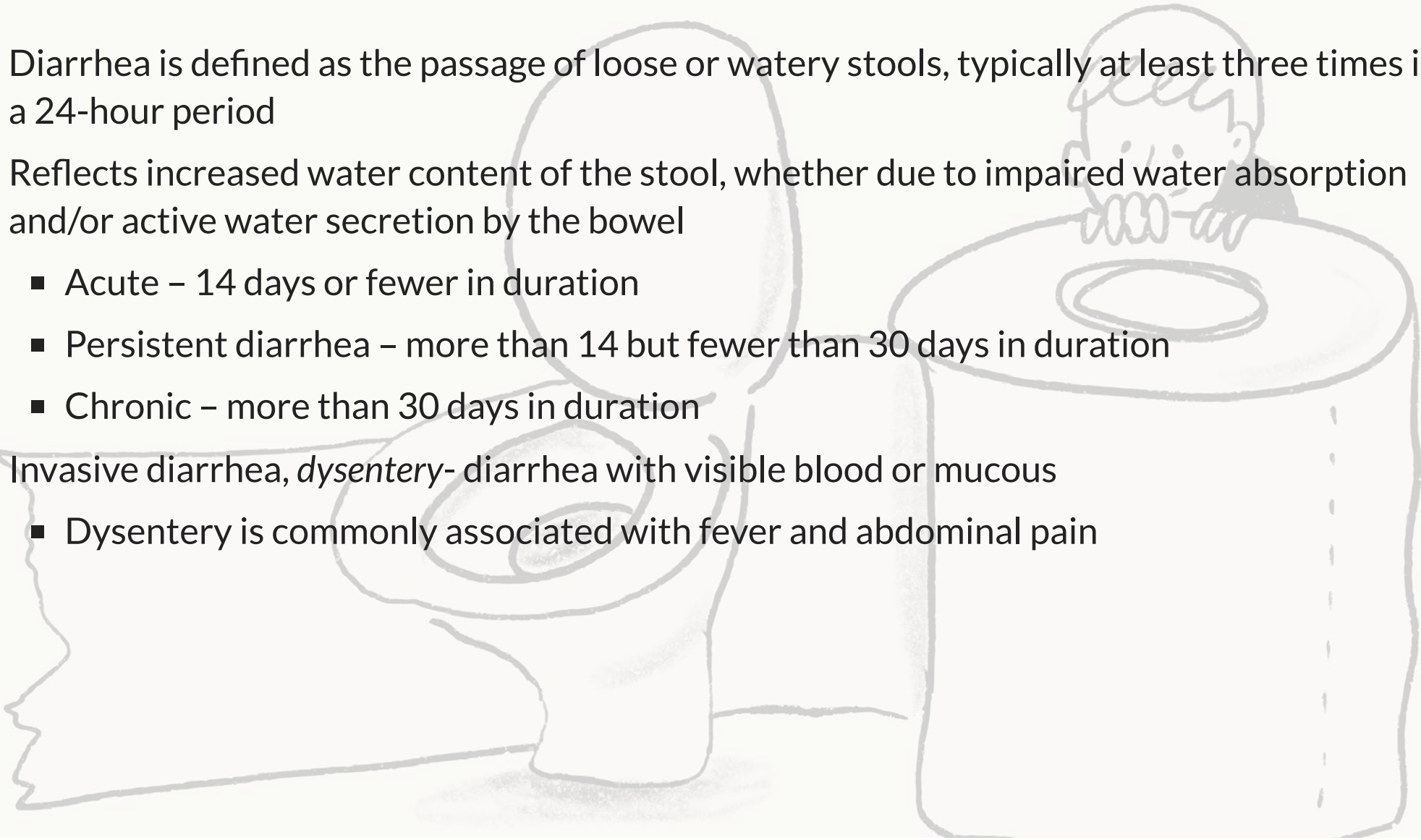
Background

- Diarrheal disease is one of the top ten leading causes of death worldwide
- Diarrheal disease is a particular concern for children younger than five years old in resource-limited settings
- Among adults in resource-rich settings, diarrhea is often a “nuisance disease” in the healthy individual
- Most cases of acute diarrhea in adults are of infectious etiology, and most cases resolve with symptomatic treatment alone
- When clinicians care for adults with diarrhea, key decision points are:
  - Determining whether this is a potentially severe manifestation that requires immediate hospitalization (patient dependent)
  - When to perform stool testing
  - Whether to initiate empiric antimicrobial therapy

(GBD 2016 Diarrhoeal Disease Collaborators, 2018; Shane et al., 2017)

Definitions

- Diarrhea is defined as the passage of loose or watery stools, typically at least three times in a 24-hour period
- Reflects increased water content of the stool, whether due to impaired water absorption and/or active water secretion by the bowel
  - Acute – 14 days or fewer in duration
  - Persistent diarrhea – more than 14 but fewer than 30 days in duration
  - Chronic – more than 30 days in duration
- Invasive diarrhea, *dysentery*- diarrhea with visible blood or mucous
  - Dysentery is commonly associated with fever and abdominal pain



General Etiology

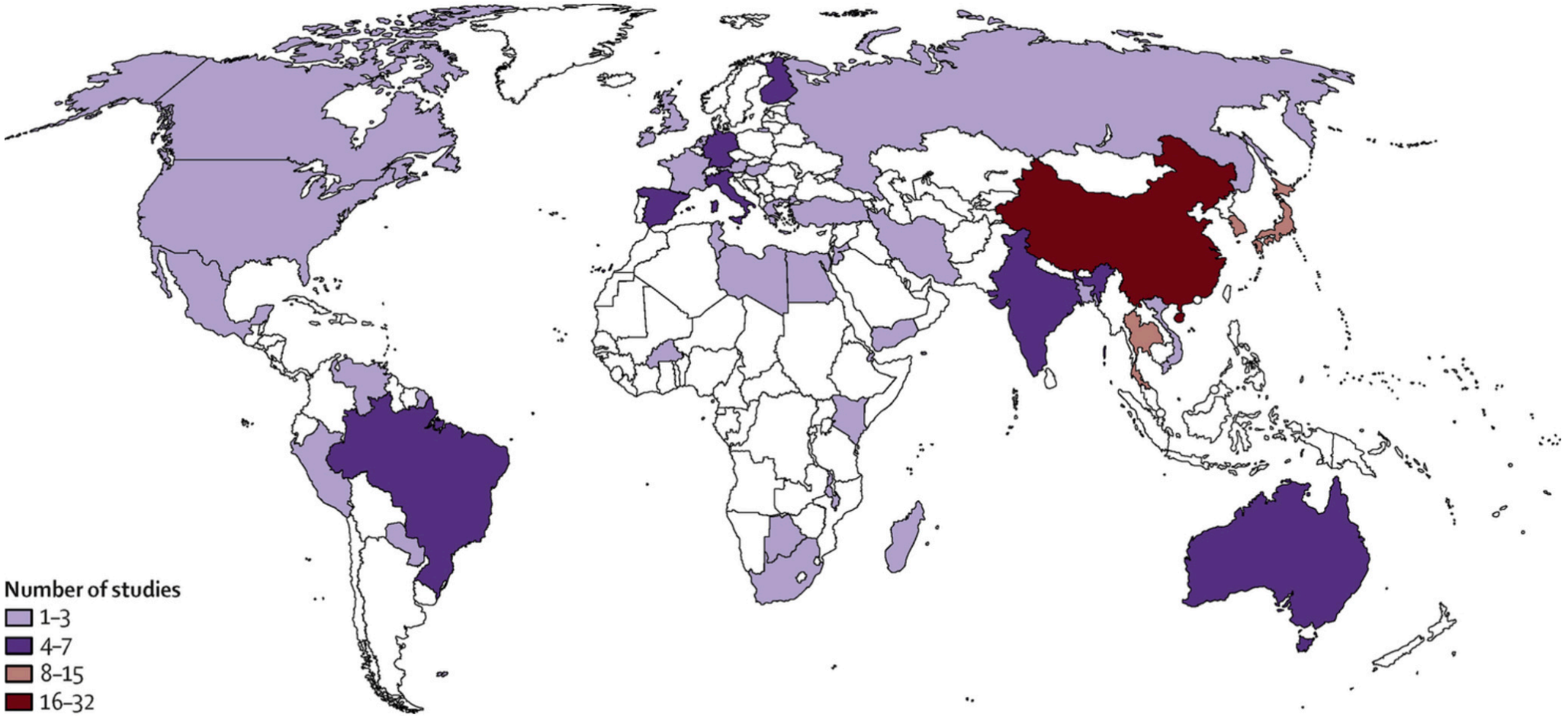
- Most cases of acute diarrhea are due to infections and are self-limited
- Most cases of acute infectious diarrhea are viral, as indicated by the observation that stool cultures are positive in only 1.5 to 5.6 % of cases
- The major causes of acute infectious diarrhea include:
  - **Viruses** (norovirus, rotavirus, adenoviruses, astrovirus, and others)
  - **Bacteria** (Salmonella, Campylobacter, Shigella, enterotoxigenic Escherichia coli, Clostridioides difficile, and others)
  - **Protozoa** (Cryptosporidium, Giardia, Cyclospora, Entamoeba, and others)

(Dryden et al., 1996)

Red flag symptoms

- Peristent stool > 1 week
- Fever > 72 hours
- Bloody diarrhea
- Severe abdominal pain
- Signs and symptoms of dehydration (tachycardia, hypotension, confusion, decreased urine output)
- Weight loss
- Recent hospital stay or antibiotic exposure
- Pregnant
- > 65 years
- Diabetic, living with HIV, or immunocompromised

Norovirus “winter vomiting virus”



(Ahmed et al., 2014)

Norovirus

- **Epidemiology**
  - Nonenveloped RNA virus from Caliciviradae family
  - Most common cause of gastroenteritis worldwide
  - Although antibody prevalence rises through childhood, re-infection is common as their is no lasting immunity due to re-infection with diversity of strains
- **Transmission**
  - Spread by fecal-oral route from person to person, aerosol in vomitus, contaminated food and water, fomite on surfaces
  - Resists killing by alcohol or chlorine, temperatures up to 60°C
  - Outbreaks are common

Norovirus

- **Clinical manifestations**:
  - Vomiting
  - Watery diarrhea, non-bloody and non-bilious, 4-8 stools/ 24 hours period
  - Fever in 50% of cases
  - Malaise, headache
  - Abdominal pain
  - Patients at risk of dehydration
  - White blood cell count elevated or normal, lymphopenia common
  - Short duration of illness (48-72 hours) with complete recovery
- **Diagnosis**:
  - Diagnosed clinically although antigen detection (enzyme immunoassay) or PCR may be used in outbreak settings.
- **Treatment**:
  - Supportive care (hydration)

Rotavirus

- Mean duration of symptoms for 3-8 days
- Occurs in children 6 months-2 years
- Occasionally causes diarrhea in elderly
- Vomiting less of a prominent feature vs. norovirus

Image: Centers for Disease Control

Enterotoxigenic *Escherichia coli* (ETEC)

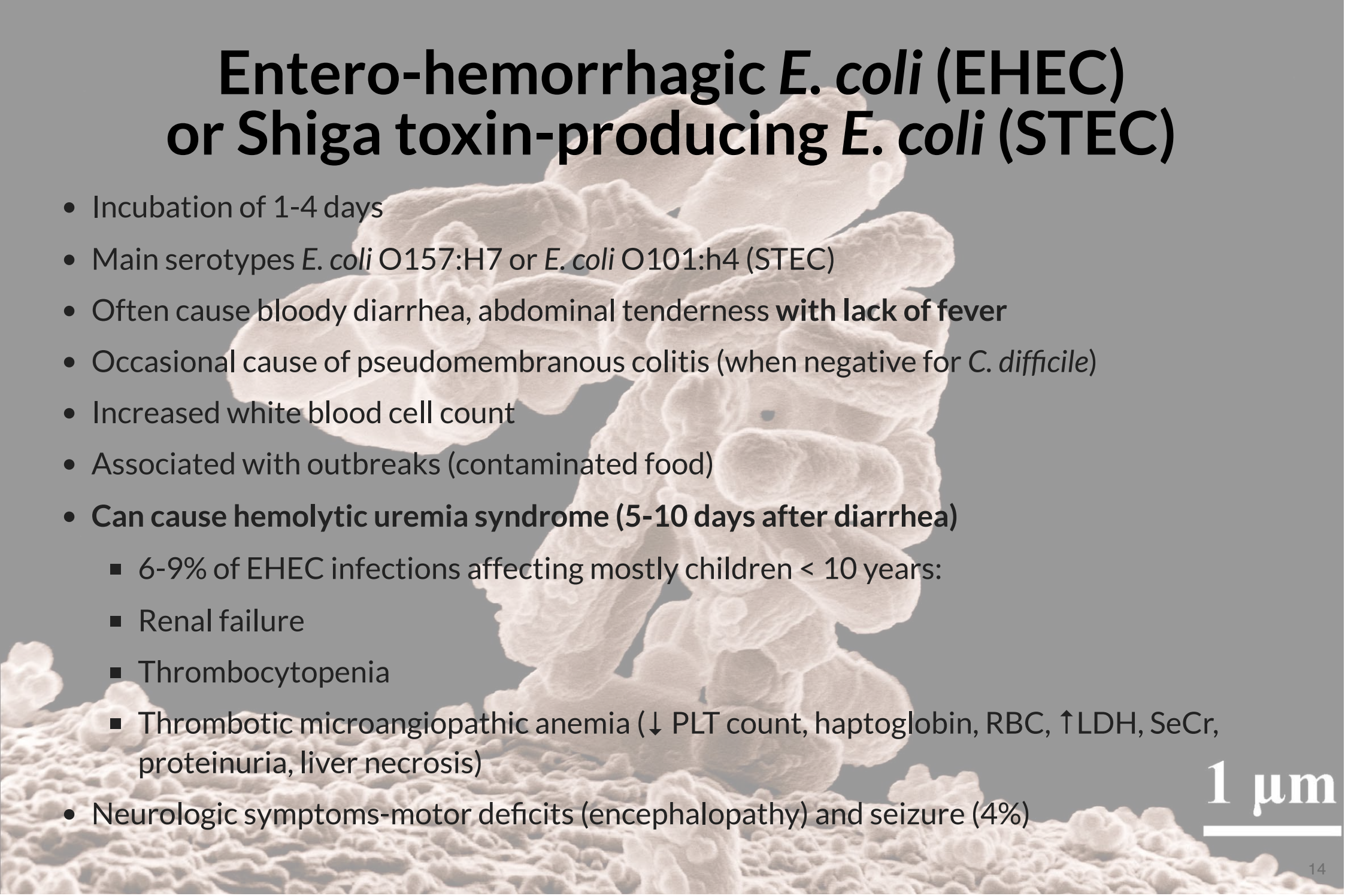
- Cause of dehydrating diarrhea , especially in developing world (< 2 years age) due to ability to survive in water and production of heat-stabile and heat-labile toxins
- Causes watery diarrhea in returning travellers **with nausea but no vomiting** and symptoms lasting as long as 5 days
- Molecular detection of genes associated with production of heat labile toxin (LT) and heat stable toxins (STh, and STp) genes]

Enteropathogenic *E. coli* (EPEC)

- Diarrhea common in children < 6 months in developing world
- Sporadic outbreaks in adults
- Severe diarrhea that can result in dehydration and malnutrition
- Molecular detection of the *eae* gene (attachment to epithelial cells)

Entero-hemorrhagic *E. coli* (EHEC) or Shiga toxin-producing *E. coli* (STEC)

- Incubation of 1-4 days
- Main serotypes *E. coli* O157:H7 or *E. coli* O101:h4 (STEC)
- Often cause bloody diarrhea, abdominal tenderness **with lack of fever**
- Occasional cause of pseudomembranous colitis (when negative for *C. difficile*)
- Increased white blood cell count
- Associated with outbreaks (contaminated food)
- **Can cause hemolytic uremia syndrome (5-10 days after diarrhea)**
  - 6-9% of EHEC infections affecting mostly children < 10 years:
  - Renal failure
  - Thrombocytopenia
  - Thrombotic microangiopathic anemia (↓ PLT count, haptoglobin, RBC, ↑LDH, SeCr, proteinuria, liver necrosis)
- Neurologic symptoms-motor deficits (encephalopathy) and seizure (4%)



EHEC toxin detection

Shiga toxin genotype*		Risk for HUS?	Representative STEC serogroups or serotypes¶	Usual appearance of diarrhea
Stx (stx) 1	Stx (stx) 2			
+	+	High	*E. coli* O26Δ, O111◊, sorbitol nonfermenting O157:H7 and O157:HNM§	Visibly bloody
–	+	High	*E. coli* O80, O104¥, O121, sorbitol nonfermenting O157:H7 and O157:HNM§, and sorbitol fermenting O157:HNM‡	Visibly bloody
+	–	Minimal or no	*E. coli* O26Δ, O103, O111◊	Non-bloody

Note that toxin genotype-serotype associations are rarely absolute, and comment is provided in footnotes if differing genotypes are common.

STEC: Shiga-toxin-producing *E. coli*; HUS: hemolytic-uremic syndrome. STEC that produce Shiga toxin 2 are much more frequently associated with severe human disease (bloody diarrhea and HUS) than those that produce only Shiga toxin 1.

¶ Serotypes designate the O (somatic) and the H (flagellar) antigens. Serogroups designate only the O antigen, which is the lipopolysaccharide side chain.

Δ European STEC O26 contain genes encoding Shiga toxins 1 and 2 and are considered high risk and are a leading cause of HUS. North American STEC O26 generally produce Shiga toxin 1 but not Shiga toxin 2. They are isolated from patients with bloody diarrhea at similar frequencies to those with nonbloody diarrhea but are almost never associated with HUS.

◊ North American STEC O111 usually produce Stx 1 but not Stx 2 but, despite lacking a gene encoding Stx 2, can be a cause of bloody diarrhea. A subset of STEC O111 contain both toxin genes and can also cause HUS.

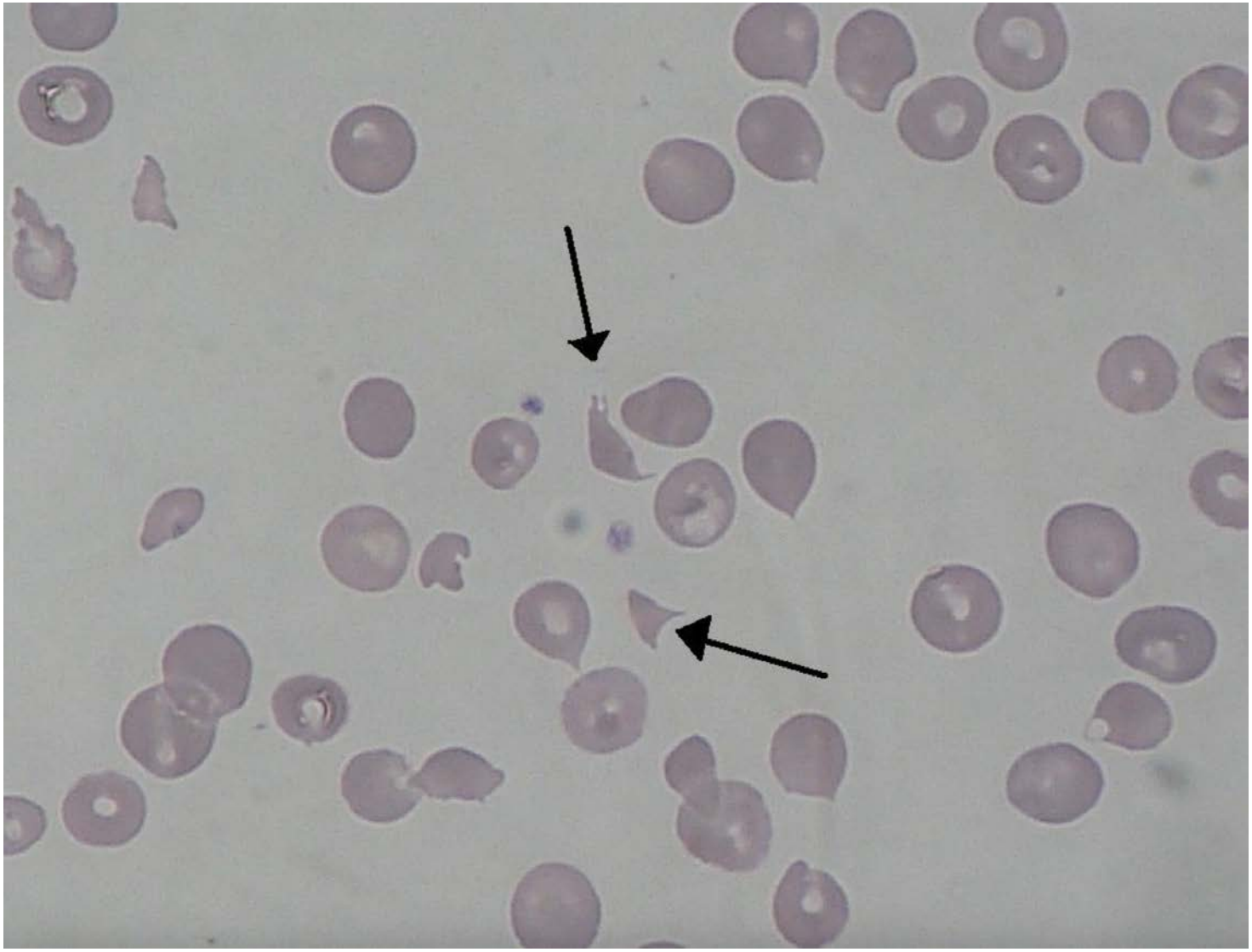
§ Occasionally, a laboratory will report that a sorbitol nonfermenting *E. coli* O157 is nonmotile, so the H antigen cannot be determined. These STEC should be considered equivalent to classic high-risk sorbitol-fermenting *E. coli* O157:H7 in virulence, even if the toxin genotype is not provided.

¥ This serogroup caused a massive outbreak in Germany and neighboring countries in 2011 but has not persisted as a major problem. It shares many features with enteroaggregative *E. coli*.

‡ This sorbitol fermenting nonmotile *E. coli* O157 is also designated *E. coli* O157:H–. It is recovered mostly in Germany and central Europe and is at least as virulent as *E. coli* O157:H7.

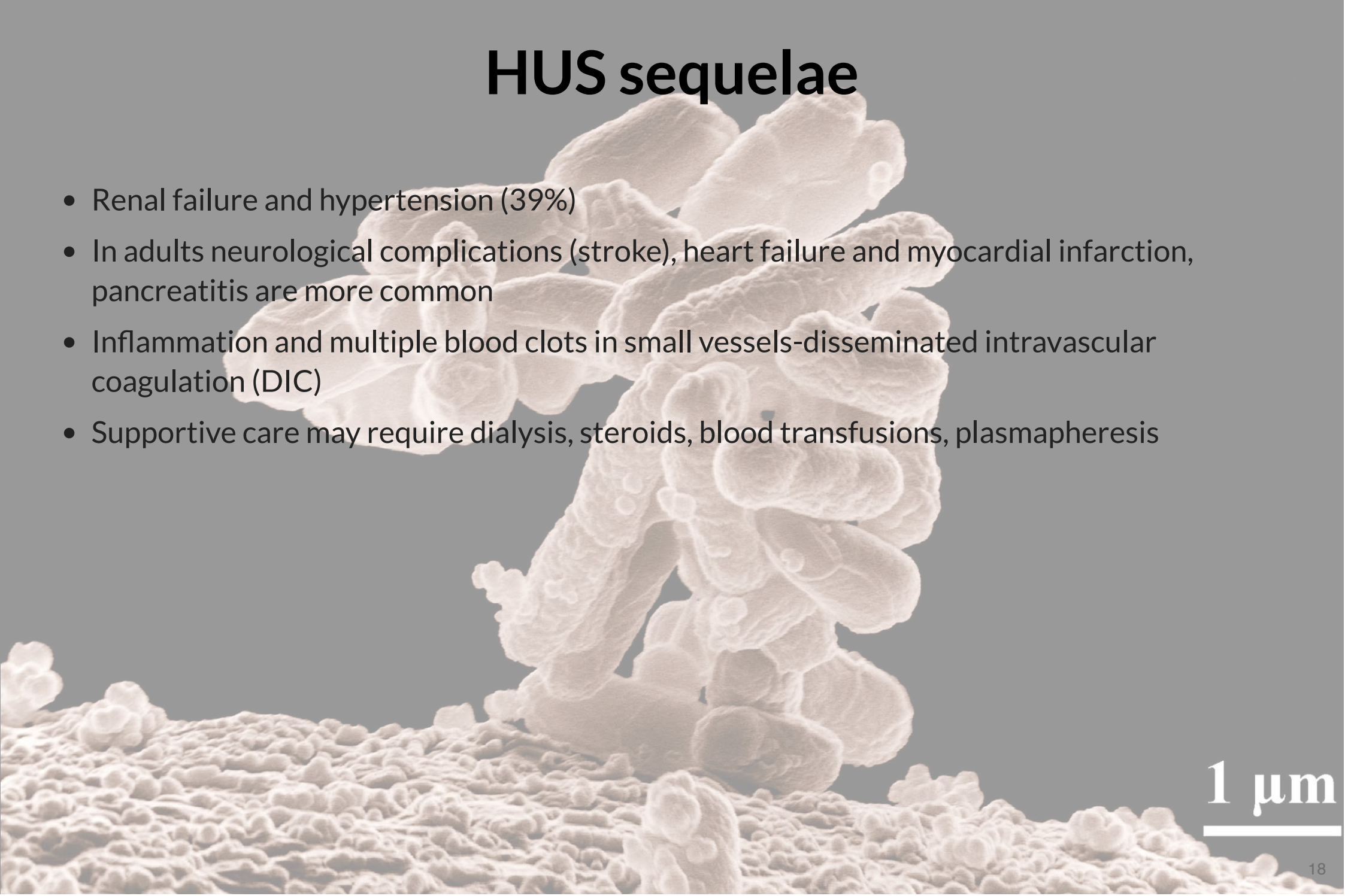
Bean sprouts

Schistocytes seen in peripheral blood with HUS



HUS sequelae

- Renal failure and hypertension (39%)
- In adults neurological complications (stroke), heart failure and myocardial infarction, pancreatitis are more common
- Inflammation and multiple blood clots in small vessels-disseminated intravascular coagulation (DIC)
- Supportive care may require dialysis, steroids, blood transfusions, plasmapheresis



Italy: E. coli 0157:H7

Italy sees most HUS cases for decades

By Joe Whitworth on March 1, 2023

Italy has reported the highest annual total of Hemolytic Uremic Syndrome (HUS) cases since records began.

From January to December 2022, 91 cases were recorded. This is the most observed in a single year since the start of surveillance in 1988. HUS is a severe complication associated with E. coli infection that causes kidney failure and can result in lifelong, serious health problems and death.

The number is still lower than in France, which recorded 128 HUS cases in 2021. This was the lowest figure since 2017 and was down from 167 in 2020. Data for 2022 is not yet available but a rise is expected due to an outbreak linked to Nestlé Buitoni Fraîch'Up brand frozen pizzas.

The Italian Haemolytic Uremic Syndrome Registry is operated by the Italian Society of Pediatric Nephrology and the Italian National Institute of Health (ISS).

How can *E. coli* O157 infection be detected?

- Culture on sorbitol MacConkey (SMAC) agar with first 6 days of bloody diarrhea
  - *E. coli* O157 cannot ferment lactose, but can ferment sorbitol
- Toxin detection (Shiga toxin, EIA in stool)
- Serotype testing 0157:H7

Why is it important to identify *E. coli* 0157 (EHEC)?

- Tracing an outbreak (i.e. contaminated produce)
- **Antibiotic therapy increases the risk of HUS in EHEC by 25% and should be avoided, especially in young children**
- Treatment with supportive measures and avoidance of anti-motility agents (e.g., loperamide) to reduce the risk of complications

Other *E. coli*- Enteroinvasive (EIEC) and Enteroaggregative (EaggEC)

- EIEC relatively rare, closely related to *Shigella*
  - Often watery diarrhea- rarely progresses to bloody diarrhea
- EaggEC
  - Affects the immunocompromised
  - Cause of persistent diarrhea in patients with HIV
  - Affects young children more frequently
  - Can often be eradicated with antibiotics

Campylobacter

- Gram-negative that belongs to the Enterobacterales (previously known as a *Vibrio*-type organism associated with abortion in cattle and sheep)
- Occurs worldwide and a leading cause of gastroenteritis, including in the Arctic and temperate areas
- *Campylobacter jejuni* most common species

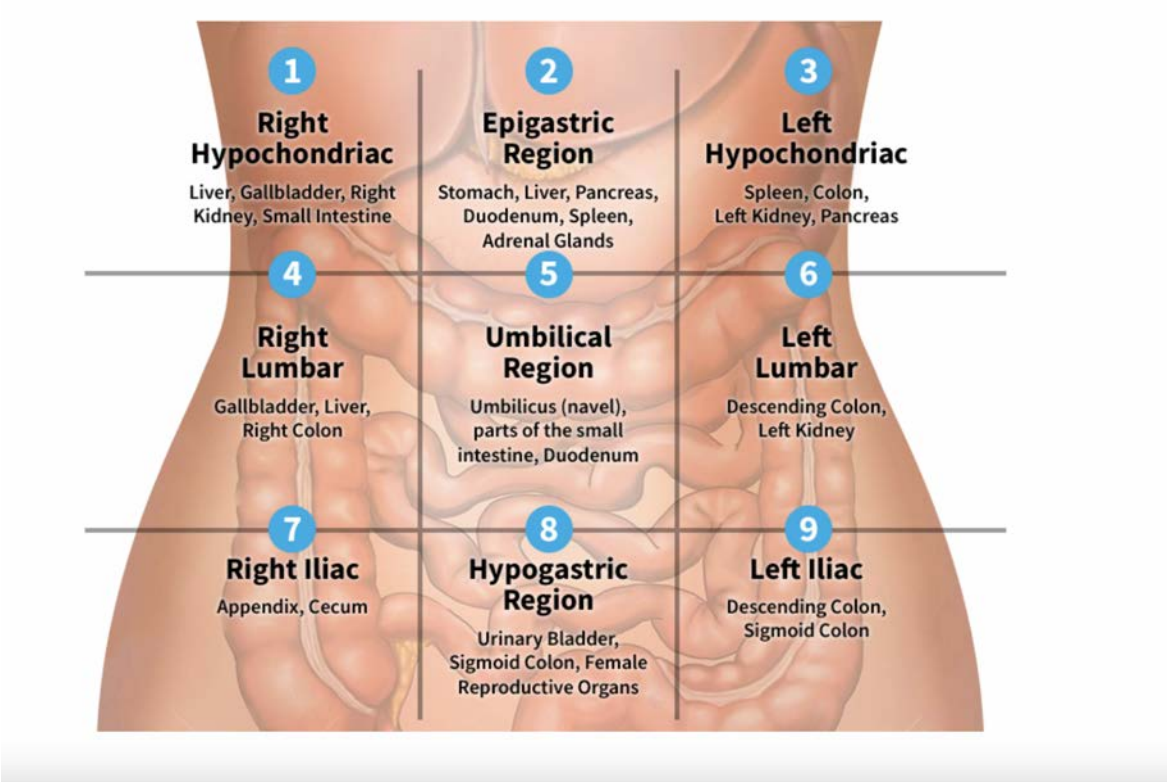
Campylobacter transmission

- Common commensal in GI tract of wild and domestic animals, **poultry** and birds
  - Food handlers: good hand hygiene essential; meat should be cooked to high temperatures (82°C, 180°F).
  - Don't drink unpasteurized milk
  - Infection can occur from eating undercooked meat
- *Campylobacter* survive in freshwater (including at temps below (15°C) → infection from swimming or drinking contaminated water
- Direct transmission from infected animals, pets, carcasses- handwashing should be encouraged especially for vulnerable adults or children visiting farms or petting zoos
- Person-to-person transmission (nursery staff working with infected children)
- Sexual transmission
- Increased infection risk in patients with increased gastric acidity (achlorhydria or proton pump inhibitor use)

Raw milk vending machine

Clinical features of Campylobacter infection

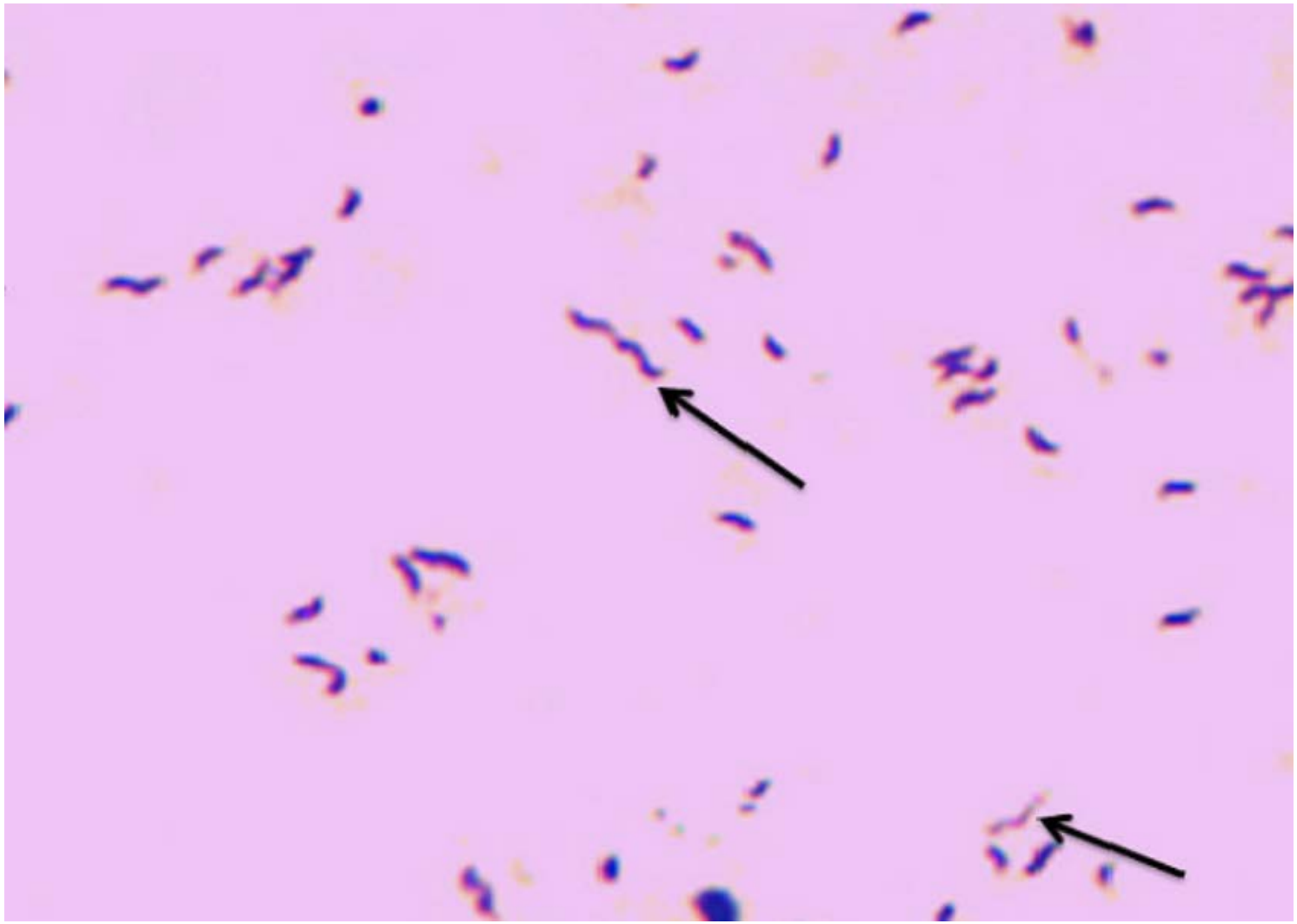
- Mean incubation 3 days (range 1-7)
- *Campylobacter* can affect either large or small bowel, hence causes both watery and bloody diarrhea
- Classic prodrome: Fevers, rigours, dizziness in 1/3 of patients prior to GI symptoms → increased severity of disease
- Abdominal pain:
  - Abrupt, severe, cramping, colicky, periumbilical- not always accompanied by diarrhea
  - Radiates to right iliac fossa in time, mimicking appendicitis and may persist after diarrhea settles
  - Nausea and vomiting (15-25% of patients)
  - Bacteremia (0.1-1%), especially immunocompromised, hypogammaglobulinemic


1
Right Hypochondriac
Liver, Gallbladder, Right Kidney, Small Intestine
2
Epigastric Region
Stomach, Liver, Pancreas, Duodenum, Spleen, Adrenal Glands
3
Left Hypochondriac
Spleen, Colon, Left Kidney, Pancreas
4
Right Lumbar
Gallbladder, Liver, Right Colon
5
Umbilical Region
Umbilicus (navel), parts of the small intestine, Duodenum
6
Left Lumbar
Descending Colon, Left Kidney
7
Right Iliac
Appendix, Cecum
8
Hypogastric Region
Urinary Bladder, Sigmoid Colon, Female Reproductive Organs
9
Left Iliac
Descending Colon, Sigmoid Colon

Campylobacter complications

- ***Guillian-Barré* disease**
  - Acute, immune-related polyneuropathy that occurs 1-2 weeks after infections
  - Linked to *Campylobacter* infection in 3-40% of cases, alterative variate called Miller-Fischer
    - 100-fold higher incidence vs. population following *C. jejuni* infection
    - Mechanism: Antibody formation that cross-reacts with GM1 ganglioside present in peripheral nerve myelin
    - Medical emergency, flaccid paralysis- 10-20% of children may require mechanical ventilation
- **Reactive arthritis**
  - Seen in 2.6% of patients, not related to severity of illness
  - Linked to HLAB27
  - Onset 1-2 weeks after infection, affecting joints, wrist, knees, ankles
  - May last for several weeks to months
  - Typically resolves, treated with non-steroidal anti-inflammatory agents (NSAIDS)

Campylobacter diagnosis



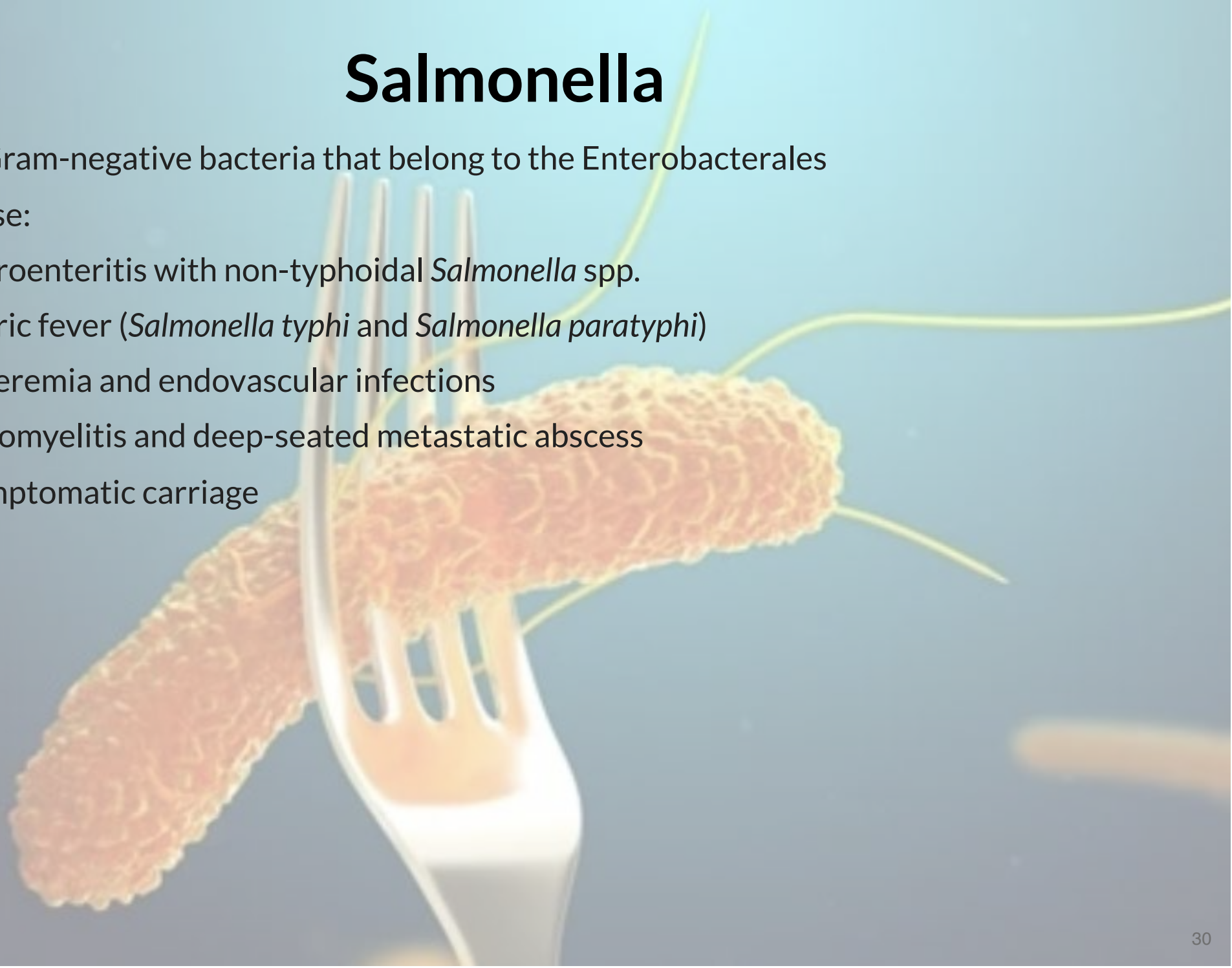
Stool culture Gram stain

Campylobacter infections: Treatment

- Generally self-limiting, antimicrobial resistance a problem (e.g., fluoroquinolone resistance in SE Asia)
- Antibiotic treatment has been shown to reduce symptoms duration by 1 day, but is indicated when patient is:
  - Immunocompromised or pregnant
  - Has severe disease with fever, bloody diarrhea, symptoms > 1 week, relapsing symptoms, or extraintestinal disease
- General approach: ciprofloxacin/levofloxacin or azithromycin x 3 days or until sings and symptoms have improved
  - 7-14 days therapy recommended in immunocompromised
- In severe infections with bacteremia or patients unable to tolerate oral medication: carbapenem + aminoglycoside

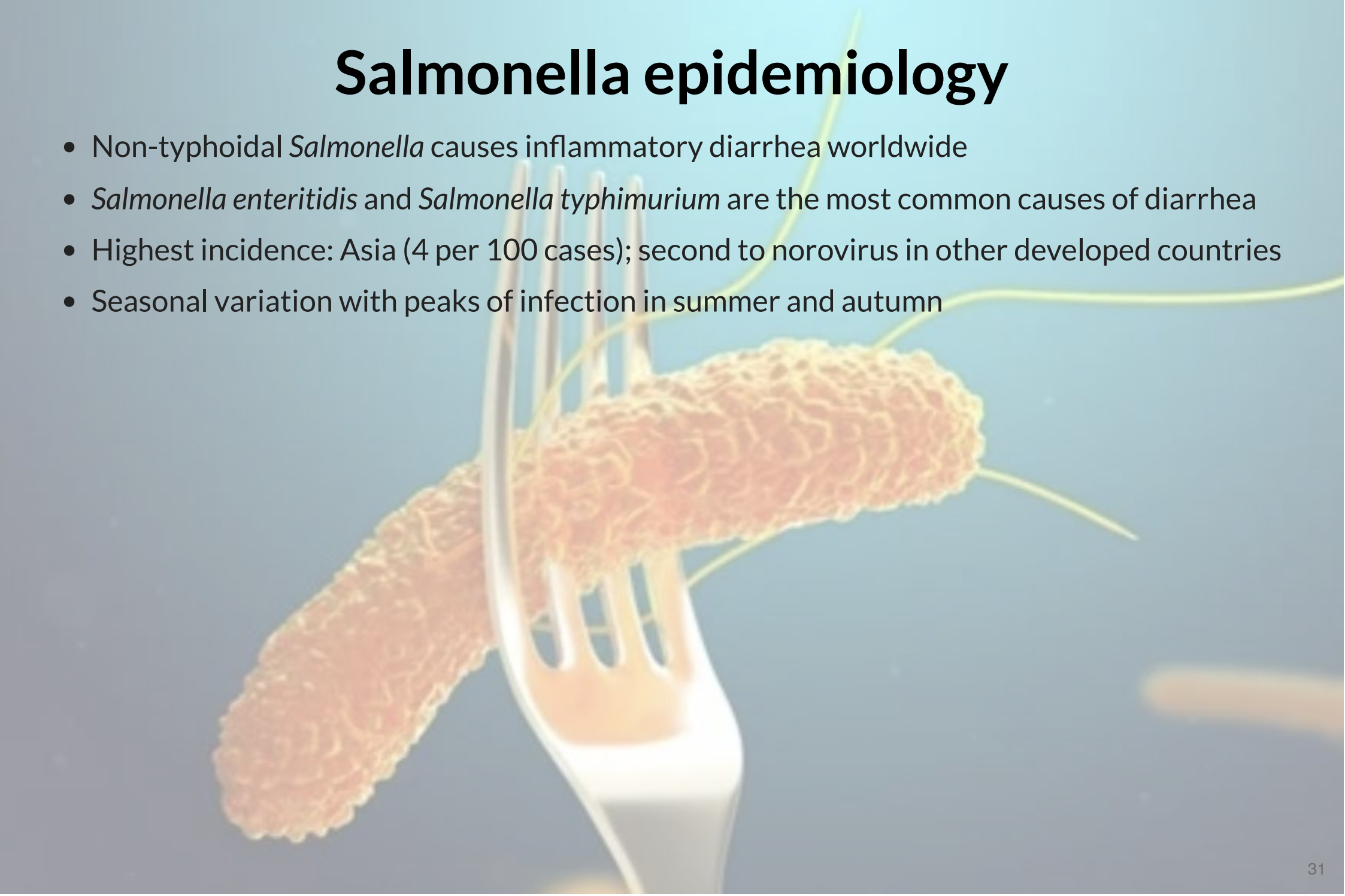
Salmonella

- Motile Gram-negative bacteria that belong to the Enterobacterales
- Can cause:
  - Gastroenteritis with non-typhoidal *Salmonella* spp.
  - Enteric fever (*Salmonella typhi* and *Salmonella paratyphi*)
  - Bacteremia and endovascular infections
  - Osteomyelitis and deep-seated metastatic abscess
  - Asymptomatic carriage



Salmonella epidemiology

- Non-typhoidal *Salmonella* causes inflammatory diarrhea worldwide
- *Salmonella enteritidis* and *Salmonella typhimurium* are the most common causes of diarrhea
- Highest incidence: Asia (4 per 100 cases); second to norovirus in other developed countries
- Seasonal variation with peaks of infection in summer and autumn

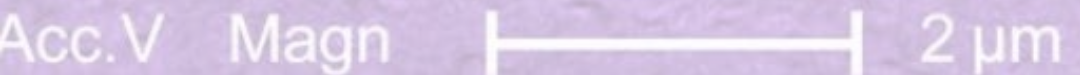


Salmonella transmission

- Feco-oral route; ingestion of poultry, eggs, and meat products including fresh produce
- Transovarial transmission can occur from infected henst to intreact egg shells, subsequently resulting in infection
- Contaminated infant milk
- Contact with animals colonized with *Salmonella* spp. (snakes, iguana, lizards, frogs, **turtles in particular**) also mice, rats , hamsters, cats, dogs, chickens, ducklings
- Petting farms and zoos
- Travel oversees and poor food and water hygiene

Clinical features

- Incubation period of 8-72 hours following ingestion of contained water/food (inoculum dependent
- Severity of symptoms related to bacterial dose- mild symptoms and asymptomatic carriage can occur
- Diarrhea with abdominal pain that resolves in 4-7 days, nausa, voming and fever generally resolve in < 72 hours
- Bloody stools in children
- Less than 5% of non-typhoidal *Salmonella* develop bactermeia
  - However, when bacteremia develops: mycotic aneurysms, abscess, osteomyelitis, infective endocarditis, endovascular infection
- Patients with achlorhydria, inflammatory bowel disease, sickle cell disease (recurrent vaso-occlusion with intestinal infarction leads to necrosis and increased gut permeability) are susceptible to more severe infection



Antibiotic treatment

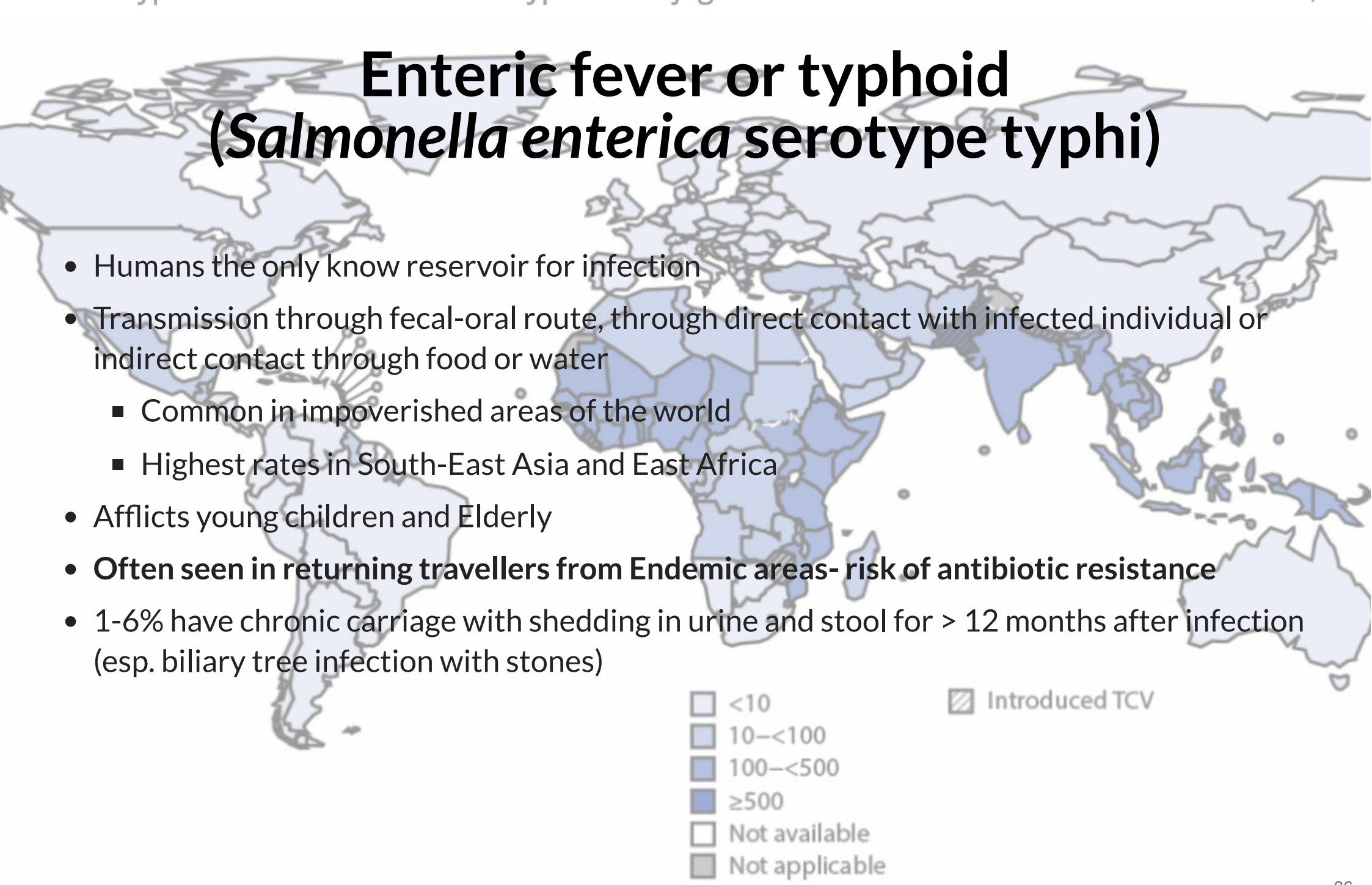
- **Guided by antimicrobial sensitivity when possible**
  - Preferred agents: fluoroquinolones (ciprofloxacin, levofloxacin) but resistance increasing
  - Alternatives: ceftriaxone, azithromycin, trimethoprim-sulfamethoxazone
- **Treatment duration:**
  - 3-7 days with severe GI disease but no bacteremia
  - 3-14 days if at risk for endovascular infections or joint complications; or older patient
- Immunosuppressed patients have problems clearing *Salmonella* because it persists in reticuloendothelial cell system (RES)- prolonged treatment is required and patients are at higher risk for metastatic infections
  - 14 days minimum to prevent infection relapsing or persisting
  - Patients with HIV with gastroenteritis may require 2-6 weeks of therapy

Asymptomatic carriage

- Compared to other serotypes, *Salmonella typhimurium* is cleared quickly (less carriage)
- Following symptomatic infection, excretion can continue fora prolonged period-5 weeks
- Shedding can be intermittent, hence several cultures are required to detect carriage
- Previous short course antibiotic therapy does not reduce carriage, and may **prolong shedding**
- **Chronic carrier states**
  - Continued shedding for over 1 year (0.6-2%)
    - More common in women, older adults, young children, biliary tract abnormalities (e.g., gallstones)- may require cholecystectomy
    - Can attempt prolonged antibiotic therapy for clearance:
      - Quinolones 4-6 weeks, *or* amoxicillin or ampicillin 6 weeks *or* trimethoprim-sulfamethoxazole for 3 months
      - Follow-up cultures after 6 months performed to confirm eradication
  - Local health policies have specific rules about return to work (food handlers, healthcare workers)

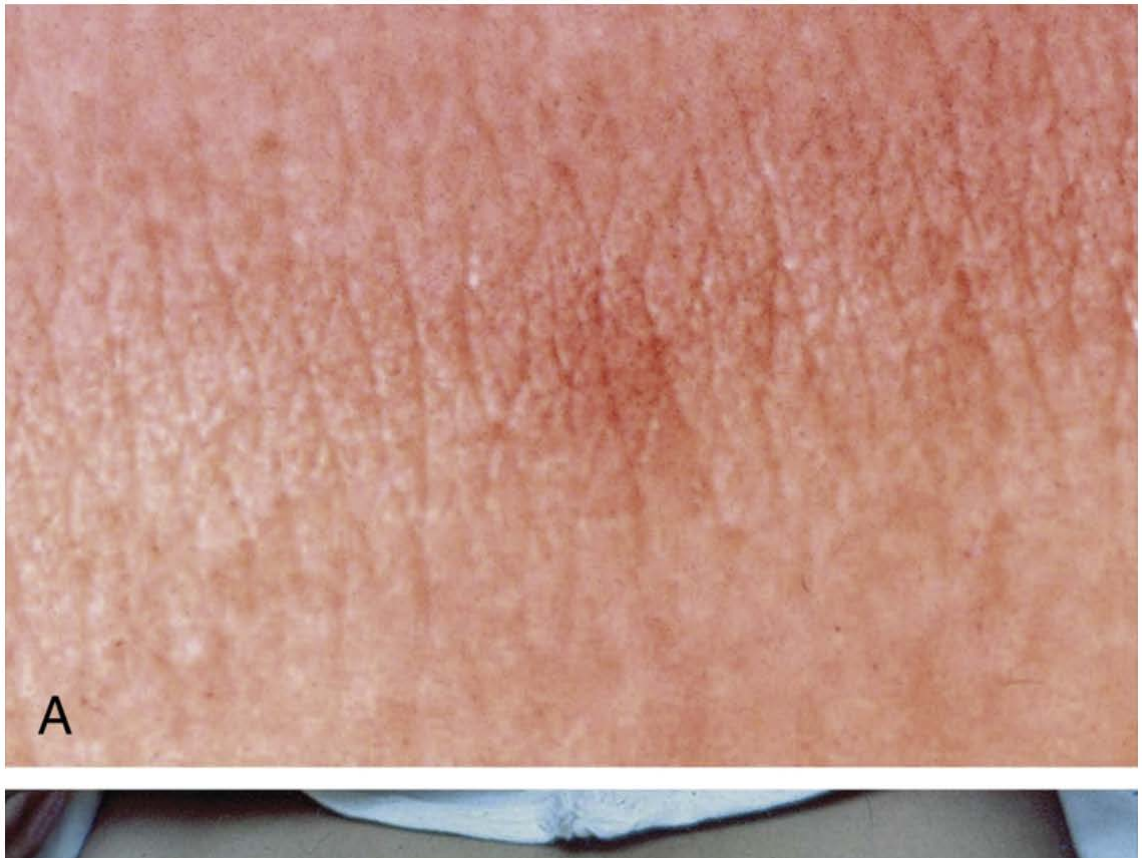
Enteric fever or typhoid (*Salmonella enterica* serotype typhi)

- Humans the only know reservoir for infection
- Transmission through fecal-oral route, through direct contact with infected individual or indirect contact through food or water
  - Common in impoverished areas of the world
  - Highest rates in South-East Asia and East Africa
- Afflicts young children and Elderly
- **Often seen in returning travellers from Endemic areas- risk of antibiotic resistance**
- 1-6% have chronic carriage with shedding in urine and stool for > 12 months after infection (esp. biliary tree infection with stones)



Clinical features of enteric fever-1

- **Stepwise over a series of weeks:**
  - **Week 1:** Fevers > 40°C with bacteremia, chills, rigours, bradycardia with pulse temperature disassociation (see FUO lecture)
    - Patients may *initially* present with constipation, whereas diarrhea is more common in children and patients living with HIV
  - **Week 2:** Abdominal pain, "rose spots"



Clinical features of enteric fever-2

- **Week 3:** Some patients can progress to abdominal perforation secondary to necrosis and lymphatic hyperplasia of Peyer's patches (uncommon in children < 5 years), hepatosplenomegaly, intestinal bleeding and secondary bacteremia → septic shock
  - Extraintestinal manifestations: headache 44-94% "typhoid encephalopathy", altered sleep patterns, myelitis, acute psychosis, signs of upper neuron disease, ataxia, parkinsonism (but meningitis is rare)
  - Bacteremia can be seen wiht involvement of cardiovascular, hepatobiliary, respiratory, genitourinary and musculoskeletal system
  - Laboratory findings: leukopenia with anemia, but leukocytosis seen in children or with intestinal perforation
- Most patients resolve the infection in weeks to months without antibiotic therapy (cause of FUO) although death can occur with abdominal perforation

How to establish typhoid fever diagnosis?

- Blood and stool cultures (blood positive in 40-80%; stool 30-40%)
- Bone marrow > 90% recovery- considered for complicated cases or if unresponsive to treatment (will remain positive at least 5 days after antibiotic treatment)
- Serology (anti-S. typhi antibiotics) less frequently used

Typhoid fever treatment

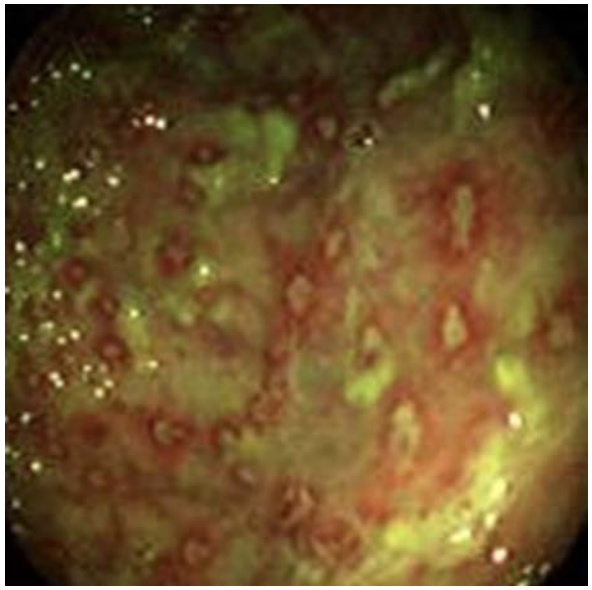
- Fluorquinolone and 3rd generation cephalosporin resistance increasing in SE Asia
- However, most strains still susceptible to 3rd generation cephalosporins and azithromycin, treatment of 10-14 days required
  - If no resistance suscepted, ciprofloxacin, which is bactericidal and concentrates intracellularly and in the bile will results in more rapid intraceiilar clearnace than beta-lactams
  - Alternatives azithromycin (5 days), ampicillin, trimimethoprim-sulfamathoxazole
- In uncomplicated cases, patients will defervesce in 4-6 days
- Relapse usually occurs after 2-3 weeks following fever resolution (depending on antibiotics) and requires further antibiotic treatment

Shigella

- Nonmotile Gram-negative facultative anaerobic bacteria belonging to Enterobacterales
  - *S. dysenteriae* (Serogroup A)
  - *S. flexneri* (Serogroup B)
  - *S. boydii (*Serogroup C)
  - *S. sonnei* (Serogroup D)
- 3rd most common cause of gastroenteritis after *Salmonella* and *Campylobacter*
- Humans are the only known host and reservoir (spread from infected food water-fecal-oral)
- Sexual transmission (anal intercourse) and epidemiologically linked to azithromycin resistance

Clinical features of Shigella infections

- Invade the colon mucosa cells causing abscess formation and ulceration
- Spread from cell to cell and produce enterotoxcins (plasmid-encoded ShET2), chromosomally-encoded ShET (S. flexneri) and shiga toxicn (Stx) (*S. dysenteriae)*
  - Toxins result in loss of water and solutes
  - Cause HUS similar to E.Coli O157 (Stx toxin)- 8% of children



Diagnosis and treatment of Shigella infections

- Best culture yield from mucous stool
- PCR testing of Stx gene
- White blood cells and red blood cells commonly seen by microbiology
- PCR testing of Shigella, but culture important for susceptibility testing
  - Asia and Africa: 20-30% resistance; TMP/SMX 65-85%
  - Antibiotic decrease duration of shedding and symptoms by 2 days
- Most infections are self limiting, but antibiotics are considerd for:
  - Immunocompromised, including patients living with HIV
  - Bacteremia or extraintestinal disease
  - Patients at risk transmitting to others (Food handlers, residential home workers, nursery staff)
- Drug of choice (no resistance concerns): fluoroquinolone; or ceftriaxone pending susceptibilities

Yersina

- Yersiniosis, causes by *Yersinia entercolitica* or *Yersinia pseudotuberculosis* is a zoonotic infection
- Associated with unpasteurized milk, undercooked meat (especially pork), water contaminated with feces- pigs are common source of infection
- After ingestion, organism proliferates in lymphoid tissue of small intestine where it may cause hyperemia, neutrophil infiltration and ulceration
- Patients may present with pharyngitis (20%)- not seen with other causes of gastroenteritis
  - Throat cultures may be positive

Yersina presentation

- Incubation period 1-14 days
- Localization of pain to right lower quandrant may be a diagnostic clue
- Hematogenous spread can lead to abscess formation in the liver, spleen, mesenteric adenitis, terminal ileitis, pseudoappendicitis
- Post-infectious immunologic sequela (reactive arthritis, erythyma nodosum)
- No established data that antibiotic treatment is beneficial for uncomplicated disease, fluoroquinolones may be given- IV ceftriaxone or ciprofloxacin in septic patients

Vibrio

- Natural inhabitants of brackish and salt water worldwide
- Diarrhea causing species are:
  - *Vibrio cholerae* (causative agent of cholera)
    - Epidemic: *V. cholerae* O1 (classical and El Tor)
      - New Serogroup 0139 Bengal merged from Southern India
  - *Vibrio parahaemalyticus*
  - *Vibrio vulnificus* (can cause diarrhea, but isolated more frequently from blood and tissues of patients with liver disease)

Vibrio transmission

- Feco-oral transmission
- Cholera outbreaks are most often associated with contaminated water and contaminated food, particuliarly undercooked or raw seafood
- *V. cholerae* O1 and O139 are producers of cholera toxin (CT)

John Snow, London

https://upload.wikimedia.org/wikipedia/commons/e/e0/Dr_John_Snow_%2824023399742%29.jpg

Vibrio clinical features

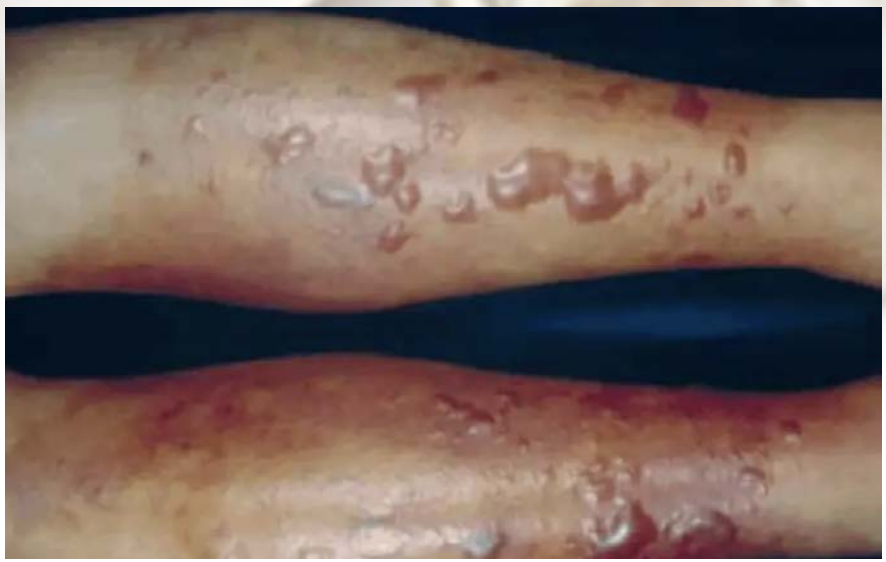
- Profuse, watery diarrhea “rice water stool”
- Mucous, but no blood present
- Incubation: A few hours to a few days
- Significant hypovolemia and electrolyte abnormalities can occur within a few hours of symptom onset
- Abdominal discomfort, borborygmi, and vomiting are common

Vibrio treatment

- Antibiotics shorten the duration of diarrhea, reduce the volume of stool losses, and decrease the duration of *V. cholera* shedding
- Treatment options include macrolides, fluoroquinolones, tetracyclines based on local resistance profile

Vibrio vulficans

- Ingestion of shellfish may give rise to cellulitis and bullous lesions (especially in cirrhotic patients)
- Especially in water temperatures above 20°C-basis of *only eat raw oysters in months that end with "R"*
- Infection can progress to invasive disease with bacteremia and systemic disease in immunosuppressed, those with cirrhotic disease or hemochromatosis
- High mortality rate with septicemia- exceeds 90% if patients present with hypotension
- Patients require immediate antibiotic therapy (tetracycline + 3rd generation cephalosporin) and transfer to the ICU - Fluoroquinolone monotherapy alternative



Clostridioides (formally Clostridium) difficile

- Will be discussed separate lecture in greater detail
- Gram-positive anaerobic bacillus that is spore forming and able to produce toxin
- *C. difficile* causes an antibiotic-associated inflammatory colitis and in the commonest cause of healthcare-associated diarrhea
- Infection requires spores to be acquired and for gut microbiota to be disrupted, usually through preceding antibiotic therapy
- Toxin A causes inflammation with intestinal fluid secretin and damage to mucosa
- Toxin B, more potent than Toxin A, acts as a virulence factor
- Diagnosis is established with 2-step process: glutamate dehydrogenase (GDH) and PCR testing or other NAAT for toxin
- Treatment: Oral vancomycin or fidoxamine > metronidazole

Others

- Aeromonas
- Plesiomonas shigelloides
- Listeria (1% but associated with outbreaks in summer-high risk foods, unpasteurized milk
  - Can cause invasive disease in pregnant and immunocompromised
  - Oral amoxicillin or trimethoprim/SMX

Parasites

- Consider if diarrhea lasts > 14 days
- Giardia, Cyclospora, Cryptosporidium spp. most common
- May be associated with community water-borne outbreaks
- Diagnosed by stool culture and examination for ova, cysts and parasites
  - Shed intermittently: May need 3 consecutive samples

Toxins

- *Clostridium perfrigens* spores poorly cooked or stored meat
  - Type A : cause of outbreaks- infection through poorly heated food and meat products (spores survive reheating)
  - Types B and D do not produce disease
  - Type C : Hemorrhagic necrosis of the jejunum (pigbel disease) following consumption of pork products. Trypsin inhibitors in sweet potatoes may inhibit breakdown of toxin and potentiates the disease
- *Staphylococcus aureus* toxin
- *Bacillus cereus* (rice) toxin

Scombroid

- Food poisoning associated with seafood
- Commonly misdiagnosed as allergy
- Incorrect storage above 4°C, resulting in bacterial overgrowth and build up of toxic levels of histamine and other biogenic amines by the bacterial enzyme histidine decarboxylase found in dark fish meat
  - Scombridae and Scoberesocidae: tuna (even open cans), mackerel, skip-jack, bonito, dolphin, tilapa, salmon, swordfish, trout, sardines
- Histamine is not broken down by cooking, freezing
  - Storing fish at 20°C for 2-3 hours is enough to result in poisoning
- Bacteria responsible for histamine accumulation: E. coli, K. pneumoniae, halophilic Vibrio sp., Proteus, Clostridium and Salmonella, and Shigella
- Fish appear to have honey-combed scales and taste “peppery”, “bubbly” or “spicy”
- Raw milk contaminated before production of Swiss cheese results in similar bacterial overgrowth and histamine build-up

Scombroid rash

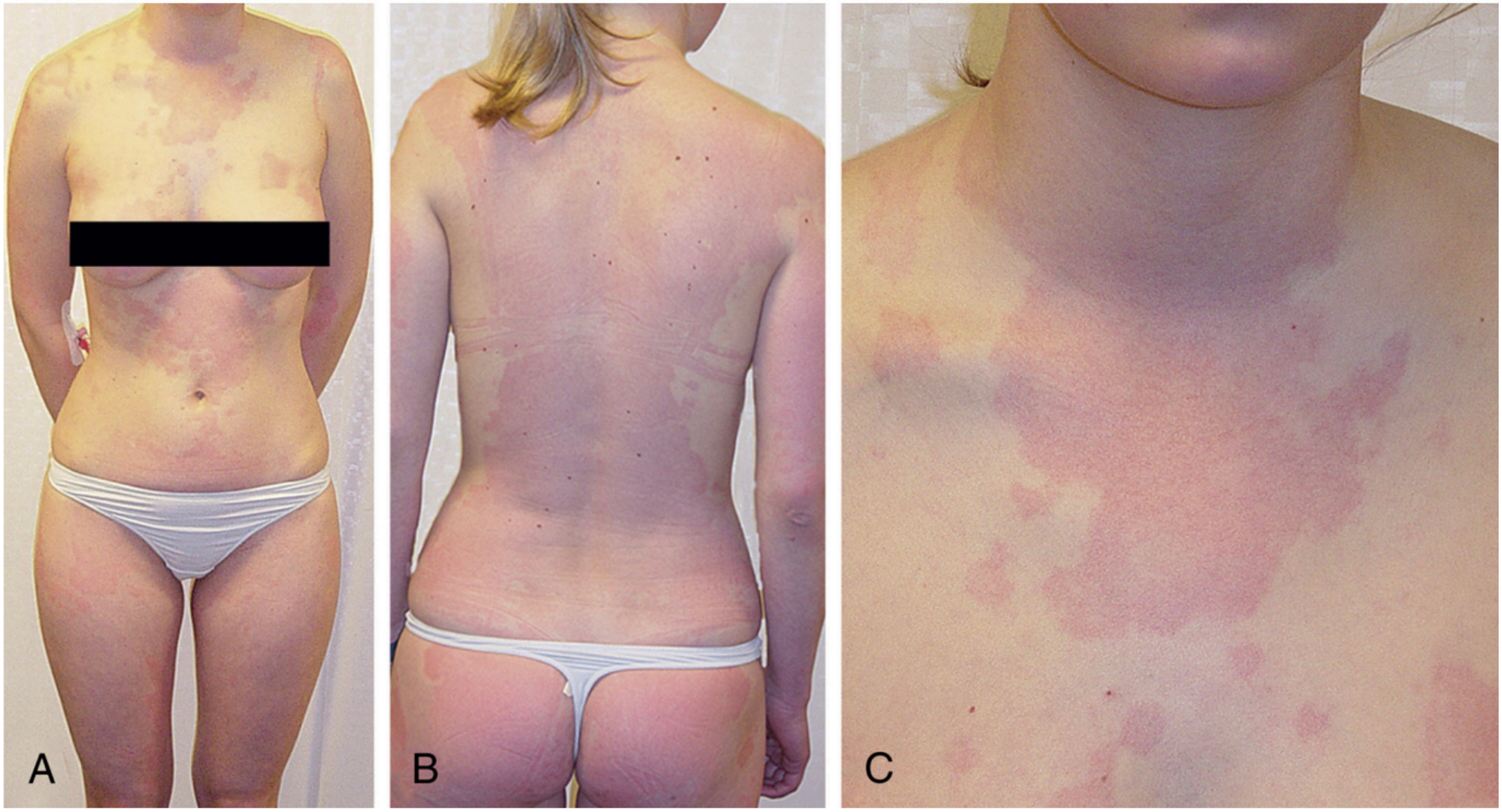


FIG. 16.7 Scombroid rash. (A and B) Widespread erythematous rash predominantly on the face (not shown) and trunk of patient 1. (C) Close-up view of the upper chest area. Note the absence of wheals.

Spec et al. Comprehensive review of infectious diseases

Ciguatera

- Foodborne illness caused by consumption of reef fish (barracuda, amberjack, moray eel, some types of grouper, snapper, parrotfish) contaminated with multiple toxins, including ciguatera toxin, which arises from dinoflagellates
- Toxins accumulate in flash and organs
- Do not look, smell or taste different unlike scombroid poisoning
- Presents with GI symptoms and neurologic signs without altered mental status

Management summary

Evaluation of acute diarrhea in adults

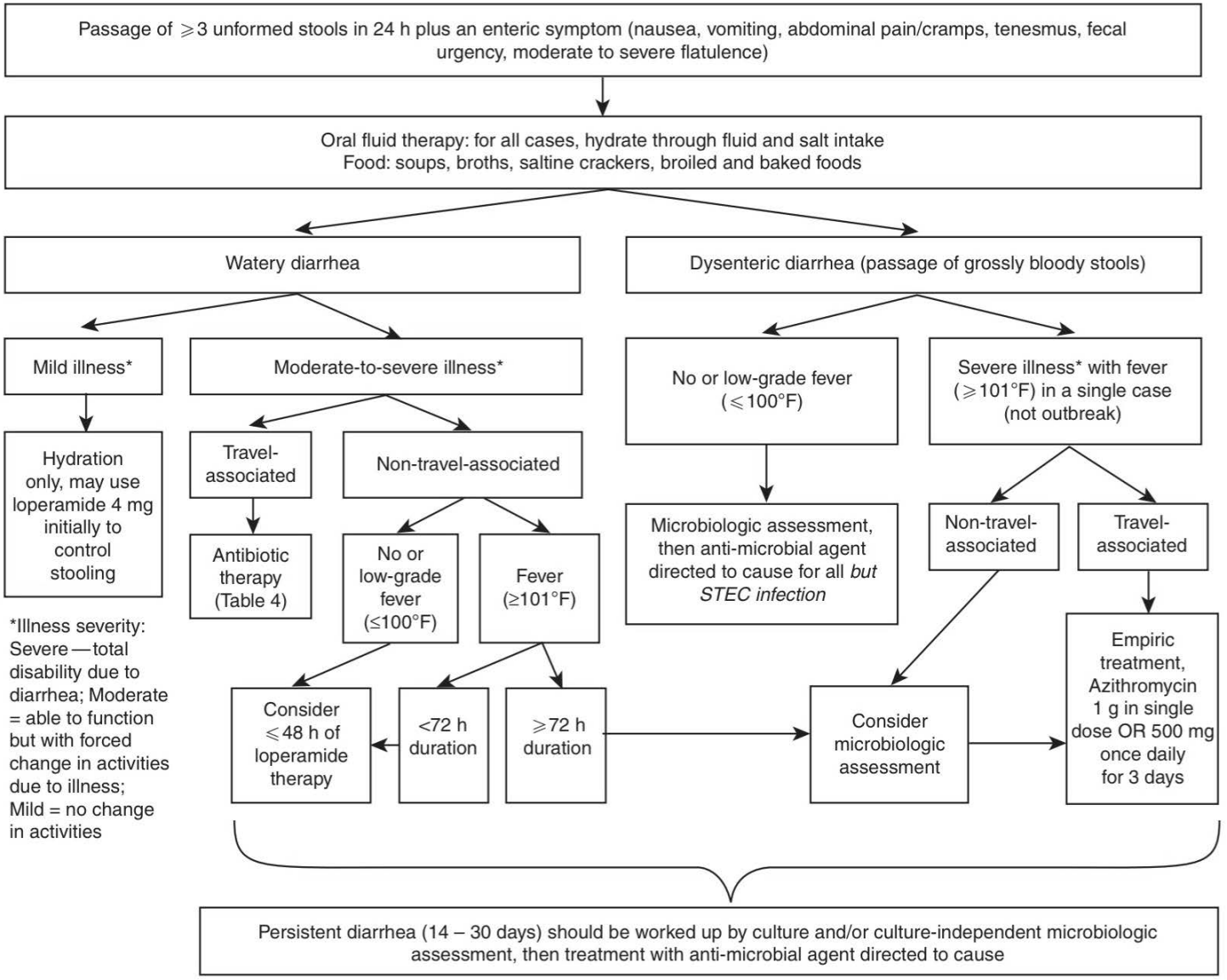


Figure 1. Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology).

(Riddle et al., 2016)

Antibiotic recommendations

Table 4. Acute diarrhea antibiotic treatment recommendations

Antibiotic[a]	Dose	Treatment duration
Levofloxacin	500 mg by mouth	Single dose[b] or 3-day course
Ciprofloxacin	750 mg by mouth or	Single dose[b]
	500 mg by mouth	3-day course
Ofloxacin	400 mg by mouth	Single dose[b] or 3-day course
Azithromycin[c,d]	1,000 mg by mouth or	Single dose[b]
	500 mg by mouth	3-day course[d]
Rifaximin[e]	200 mg by mouth three times daily	3-days

ETEC, Enterotoxigenic *Escherichia coli*.

[a]Antibiotic regimens may be combined with loperamide, 4 mg first dose, and then 2 mg dose after each loose stool, not to exceed 16 mg in a 24-h period.

[b]If symptoms are not resolved after 24 h, complete a 3-day course of antibiotics.

[c]Use empirically as first line in Southeast Asia and India to cover fluoroquinolone-resistant *Campylobacter* or in other geographical areas if *Campylobacter* or resistant ETEC are suspected.

[d]Preferred regimen for dysentery or febrile diarrhea.

[e]Do not use if clinical suspicion for *Campylobacter*, *Salmonella*, *Shigella*, or other causes of invasive diarrhea.

(Riddle et al., 2016)

When should patient be evaluated in clinic?

- Symptoms:
  - Persistent fever
  - Bloody diarrhea
  - Severe abdominal pain
  - Symptoms of volume depletion (eg, dark or scant urine, symptoms of orthostasis)
  - History of inflammatory bowel disease
  - Hospitalization should be considered:
  - History of immunosuppression (e.g., treatment for malignancy, transplantation, HIV
  - Significant cardiovascular diseases

Extraintestinal manifestations

Manifestation	Pathogen
Aortitis, osteomyelitis, deep tissue infection	*Salmonella*, *Yersinia*
Intestinal perforation	*Salmonella*, including *Salmonella Typhi*, *Shigella*, *Campylobacter*, *Yersinia*, *Entamoeba histolytica*
Postinfectious irritable bowel	*Campylobacter*, *Salmonella*, *Shigella*, *STEC*, *Giardia*
Hemolytic anemia	*Campylobacter*, *Yersinia*
Immunoglobulin A nephropathy	*Campylobacter*
Glomerulonephritis	*Shigella*, *Campylobacter*, *Yersinia*
Hemolytic uremic syndrome	*STEC*, *Shigella dysenteriae* serotype 1
Erythema nodosum	*Yersinia*, *Campylobacter*, *Salmonella*, *Shigella*
Reactive arthritis	*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, rarely *Giardia*, and *Cyclospora cayetanensis*
Meningitis	*Listeria*, *Salmonella* (infants ≤3 months of age are at high risk)
Guillain–Barré syndrome	*Campylobacter*

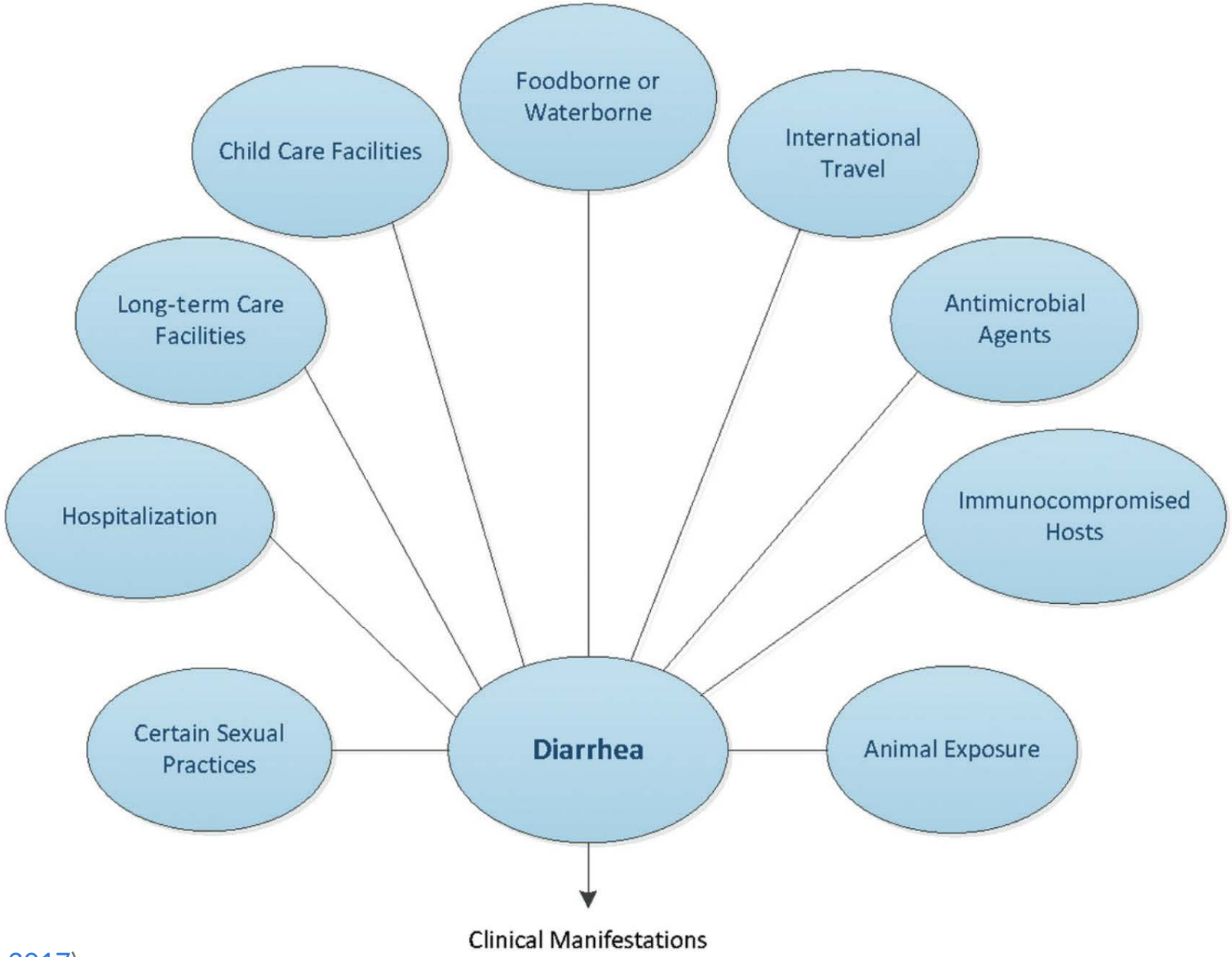
Causes of acute infectious diarrhea in adults in resource-rich settings

	Likely pathogens	Mean incubation period	Classic/ common food sources	Other epidemiologic clues
Watery diarrhea	Norovirus	24 to 48 hours	-Shellfish, prepared foods, vegetables, fruit	Outbreaks in: - Restaurants - Health care facilities - Schools and childcare centers - Cruise ships - Military populations
Clostridioides (formerly *Clostridium difficile*)	N/A	N/A	Antibiotic use - Hospitalization - Cancer chemotherapy - Gastric acid suppression - Inflammatory bowel disease	
Clostridium perfringens	8 to 16 hours	Meat, poultry, gravy, home-canned goods		
Enterotoxigenic *Escherichia coli* (ETEC)	1 to 3 days	Fecally contaminated food or water	-Travel to resource-limited settings	
Other enteric viruses (rotavirus, enteric	10 to 72 hours	Fecally contaminated food or water	-Daycare centers -Gastroenteritis in children	

	Likely pathogens	Mean incubation period	Classic/ common food sources	Other epidemiologic clues
adenovirus, astrovirus, sapovirus)			-Immunocompromised adults	
Giardia lamblia	7 to 14 days	Fecally contaminated food or water	-Daycare centers -Swimming pools -Travel, hiking, camping (particularly when there is contact with water in which beavers reside)	
Cryptosporidium parvum	2 to 28 days	Vegetables, fruit, unpasteurized milk	-Daycare centers -Swimming pools and recreational water sources - Animal exposure -Chronic diarrhea in advanced HIV infection	
Listeria monocytogenes	1 day (gastroenteritis)	Processed/delicatessen meats, hot dogs, soft cheese, pâtés, and fruit	-Pregnancy -Immunocompromising condition -Extremes of age	
Cyclospora cayetanensis	1 to 11 days	Imported berries, herbs	-Chronic diarrhea in advanced HIV infection	
Inflammatory diarrhea (fever, mucoid or bloody stools)¶	Nontyphoidal *Salmonella*	1 to 3 days	-Poultry, eggs, and egg products, fresh produce, meat, fish, unpasteurized milk or juice, nut butters, spices	-Animal contact (petting zoos, reptiles, live poultry, other pets) -Travel to resource-limited settings
Campylobacter spp	1 to 3 days	Poultry, meat, unpasteurized milk	-Travel to resource-limited settings -Animal contact (young	

	Likely pathogens	Mean incubation period	Classic/ common food sources	Other epidemiologic clues
			puppies or kittens, occupational contact)	
Shigella spp	1 to 3 days	Raw vegetables	-Daycare centers Crowded living conditions -Men who have sex with men -Travel to resource-limited settings	
Enterohemorrhagic *E. coli* (EHEC)	1 to 8 days	Ground beef and other meat, fresh produce, unpasteurized milk and juice	-Daycare centers -Nursing homes -Extremes of age	
Yersinia spp	4 to 6 days	Pork or pork products, untreated water	-Abnormalities of iron-metabolism (eg, cirrhosis, hemochromatosis, thalassemia) -Blood transfusion	
Vibrio parahemolyticus	1 to 3 days	Raw seafood and shellfish	Cirrhosis	
Entamoeba histolytica	1 to 3 weeks	Fecally contaminated food or water	Travel to resourcelimited settings Men who have sex with	

Patient Medical History



(Shane et al., 2017)

Patient Medical History

- Duration of symptoms
- ***Frequency and characteristics of stool***
- ***Associated Symptoms***
- Evidence of extracellular volume depletion (e.g., dark of scan urine, decreased skin turgor, orthostatic hypotension)

Small Bowel vs. Colon

- Diarrhea of *small bowel* is typically:
  - Watery
  - Large volume
  - Accompanied by abdominal cramping, bloating and gas
- Diarrhea of *large intestine* is typically: - Frequent - Regular - Small volume - Painful - Bloody or mucoid stools (red blood and inflammatory cells seen in stool microscopy)
- Caveat: Patients can have both small and large bowel involvement

Small Bowel vs. Colon

Pathogen	Small bowel	Colon
Bacteria	*Salmonella* *Escherichia coli*¶ *Clostridium perfringens* *Staphylococcus aureus* *Aeromonas hydrophila* *Bacillus cereus* *Vibrio cholerae*	*Campylobacter* *Shigella* *Clostridioides difficile* *Yersinia* *Vibrio parahaemolyticus* Enteroinvasive E. coli *Plesiomonas shigelloides* *Klebsiella oxytoca* (rare)
Virus	Rotavirus Norovirus Astrovirus	Cytomegalovirus* Adenovirus Herpes simplex virus
Protozoa	*Cryptosporidium *Microsporidium* _Cystoisospor*a_ *Cyclospora* *Giardia lamblia*	*Entamoeba histolytica*

¶ EPEC, EAggEC, EHEC, ETEC may all contribute; routine laboratories and cultures will not differentiate these from E. coli which are normal flora

Inflammatory signs: large-bowel infection

Fever, bloody or mucoid stools suggest invasive bacteria (eg, *Salmonella*, *Shigella*, or *Campylobacter*), enteric viruses (eg, cytomegalovirus [CMV] or adenovirus), *Entamoeba histolytica*, or *C. difficile*.

- Bloody stools, think: Shiga toxin-producing *E. coli* (STEC) (eg, *E. coli* O157:H7) infection.
  - Other bacterial causes of visibly bloody diarrhea are *Shigella*, *Campylobacter*, and *Salmonella* species.
  - Bloody diarrhea can also reflect noninfectious etiologies such as inflammatory bowel disease or ischemic colitis.
  - Syndromes that begin with diarrhea but progress to fever and systemic complaints, such as headache and muscle aches, should raise the possibility of :
    - Typhoidal illness (particularly in travellers from resource-limited settings)
    - *Listeria monocytogenes* (particularly if a stiff neck is also present in pregnant patient)

(Riddle et al., 2016)

Medical History: Exposures

- Food history
- Residence
- Occupational exposure
- Recent and remote travel
- Pets
- Hobbies

Food history

- Consumption of unpasteurized dairy products, raw or undercooked meat or fish, or organic vitamin preparations may suggest certain pathogens.
- The timing of symptom onset following exposure to the suspected offending food can be an important clue to the diagnosis
  - **Within six hours** – suggests ingestion of a preformed toxin of *Staphylococcus aureus* or *Bacillus cereus*, particularly if nausea and vomiting were the initial symptoms
  - **At 8 to 16 hours** – suggests infection with *Clostridium perfringens*
  - **More than 16 hours** – suggests either viral or other bacterial infection (eg, contamination of food with enterotoxigenic or STEC or other pathogens)

Major foodborne microbes by the principal presenting gastrointestinal symptom

Major presenting symptom	Likely microbes	Incubation period	Likely food sources
Vomiting	*S. aureus*	1 to 6 hours	Prepared food, eg, salads, dairy, meat
	B. cereus	1 to 6 hours	Rice, meat
	Norwalk-like viruses	24 to 48 hours	Shellfish, prepared foods, salads, sandwiches, fruit
Watery diarrhea	*C. perfringens*	8 to 16 hours	Meat, poultry, gravy
	Enterotoxigenic *E. coli*	1 to 3 days	Fecally contaminated food or water
	Enteric viruses	10 to 72 hours	Fecally contaminated food or water
	C. parvum	2 to 28 days	Vegetables, fruit, unpasteurized milk, water
	C. cayetanensis	1 to 11 days	Imported berries, basil
Inflammatory diarrhea	*Campylobacter* spp	2 to 5 days	Poultry, unpasteurized milk, water
	Nontyphoidal Salmonella	1 to 3 days	Eggs, poultry, meat, unpasteurized milk or juice, fresh produce
	Shiga toxin-producing *E. coli*	1 to 8 days	Ground beef, unpasteurized milk and juice, raw vegetables, water

Major presenting symptom	Likely microbes	Incubation period	Likely food sources
Shigella spp	1 to 3 days	Fecal contamination of food and water	
V. parahemolyticus	2 to 48 hours	Raw shellfish	

Incubation period and likely food sources are shown for each.

Modified from Centers for Disease Control and Prevention. Diagnosis and management of food borne illness, a primer for physicians. MMWR Recomm Rep April 16, 2004 / 53(RR04);1-33

Other exposures

- Exposure to animals (poultry, turtles, petting zoos) has been associated with *Salmonella* infection.
- Travel to a resource-limited setting increases the risk of bacterial diarrhea and also informs the risk of certain parasitic infections
- Occupation in daycare centres has been associated with:
  - infections with *Shigella*, *Cryptosporidium*, and *Giardia*.
  - Rotavirus is a potential consideration, but decreased with vaccination

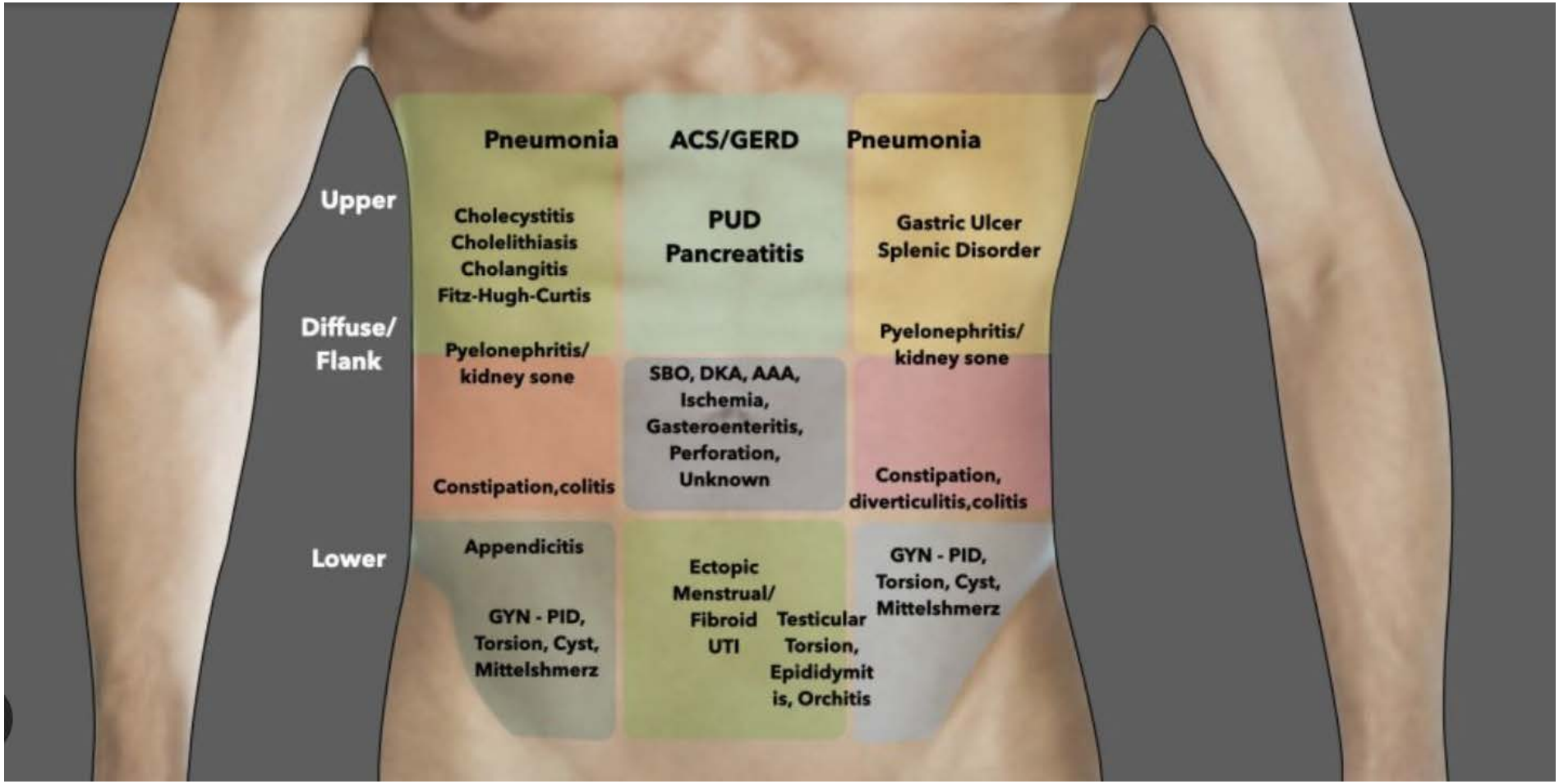
Additional Medical history

- Recent antibiotic use (as a clue to the presence of *C. difficile* infection)
- Other medications (such as proton pump inhibitors, which can increase the risk of infectious diarrhea)
- Predisposing conditions:
  - Immunocompromised host or the possibility of nosocomial infection
  - Medical history informing the likelihood of various pathogens
  - Pregnancy increases the risk of listeriosis following consumption of contaminated meat products or unpasteurized dairy products approximately 20-fold
  - Cirrhosis has been associated with *Vibrio* infection
  - Hemochromatosis has been associated with *Yersinia* infection

Physical exam-1

- **Exam focus- volume status and identifying complications**
  - Volume depletion can be suggested by:
    - dry mucous membranes
    - diminished skin turgor
    - postural or frank reductions in blood pressure
    - altered sensorium
- These signs can be mild or absent with early hypovolemia

Physical exam-2

- Abdominal examination should focus on signs that suggest ileus or peritonitis
  - Abdominal distension
  - Pain with gentle percussion
  - Abdominal rigidity, or rebound tenderness
- 

Laboratory exam

- Laboratory tests are not routinely warranted for most patients with acute diarrhea
- If substantial volume depletion is present (suggested by signs or symptoms such as dark and concentrated urine), a basic metabolic panel should be performed to screen for hypokalemia or renal dysfunction
- The complete blood count does not reliably distinguish bacterial etiologies of diarrhea from others but may be helpful in suggesting severe disease or potential complications
  - A low platelet count may prompt concern for the development of the hemolytic-uremic syndrome
  - Leukemoid reaction is consistent with the diagnosis of *C. difficile* infection.
- Blood cultures should be obtained in patients with high fevers or who appear systemically ill

When are stool cultures considered?

- **Severe illness**
  - Profuse watery diarrhea with signs of hypovolemia
  - Passage of > 6 unformed stools per 24 hours
  - Severe abdominal pain
  - Need for hospitalization
- **Other signs of symptoms concerning for inflammatory diarrhea**
  - Bloody diarrhea
  - Passage of many small stools containing blood and mucus
  - Temperature >38.5°
- **High-risk host features**
  - Age ≥ 70 years
  - Comorbidities such as cardiac disease (exacerbated by hypovolemia or complicating fluid replacement)
  - Immunocompromised condition (including advanced HIV)
  - Inflammatory bowel disease
  - Pregnancy
  - Symptoms persisting more than 1 week
- **Suspected public health issue**

Goal: Identify a potential bacterial pathogen that would inform the potential for complications and treatment decisions

Stool cultures

- The optimal specimen for culture is a diarrheal stool specimen (conforms to container)o, which should be inoculated onto culture plates as quickly as possible.
- Routine stool culture will identify *Salmonella*, *Campylobacter*, and *Shigella*
- *E. coli* O157:H7 can be isolated on sorbitol-MacConkey plates or identified with antigen testing or polymerase chain reaction of stool
- A stool culture that is positive for one of these pathogens in a patient with acute diarrheal symptoms can be interpreted as a true positive.
- If a stool specimen cannot be obtained promptly, a rectal swab culture can be obtained to accelerate the diagnosis although some data suggest decreased sensitivity in adults
- May need to specify bacteria of interest
    - Campylobacter
    - Aeromonas, Yersina
    - Vibrio-requires selective media
- Bacterial pathogens are generally excreted continuously, in contrast to ova and parasites, which are often shed intermittently.
- **Thus, a negative culture is usually not a false negative, and repeat specimens are rarely required.**

Stool testing: molecular methods

- Multipathogen molecular panels — Some laboratories have access to multiplex stool tests, with which molecular tests for a panel of many different pathogens (bacterial, viral, and parasitic) can be performed simultaneously on diarrheal stool samples and, in some cases, rectal swab

Treatment

- Antibiotic specific recommendations per pathogen.
  - Fluroquinolones, azithromycin, ceftriaxones (amoxicillin), trimethoprim-sulfamethoxazole, doxycycline
- Oral rehydration when possible vs. IV

Fluid repletion

- The most critical therapy in diarrheal illness is rehydration, preferably by the oral route, with solutions that contain water, salt, and sugar
- Diluted fruit juices and flavored soft drinks along with saltine crackers and broths or soups may meet the fluid and salt needs in patients with mild illness
- The electrolyte concentrations of fluids used for sweat replacement (eg, Gatorade) are not equivalent to oral rehydration solutions, although they may be sufficient for the otherwise healthy patient with diarrhea who is not hypovolemic.
- Oral rehydration solutions (ORS), including standard World Health Organization ORS or commercial ORS, such as Rehydralyte and Ceralyte, may be more appropriate in patients with more severe diarrheal disease. They should be used both to replete a volume depleted patient and also to maintain adequate volume status once replete.

Composition of oral rehydration solutions (ORSC) and commonly used beverages

Sodium	Potassium	Base (HCO3–)		
Oral rehydration solutions				
CeraLyte	40	70	20	10	235
Enfalyte	30	50	25	30	200
Pedialyte	25	45	20	30	250
Rehydralyte	25	75	20	30	310
WHO (1975)	20	90	30	30	310
WHO (2002)	13.5	75	20	30	245

	Carbohydrate (g/L)	mEq/L			Osmolarity (mOSM/kg H2O)
Commonly Used Beverages (not appropriate for repletion therapy)					
Apple juice	100 to 150	3	20	0	700
Chicken broth	0	250	5	0	450
Colas	100 to 150	2	0.1	13	550
Gatorade	45	20	3	3	330
Ginger Ale	90	3.5	0.1	3.6	565
Tea	0	0	0	0	5

ORSs were developed following the realization that, in many small bowel diarrheal illnesses,

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