
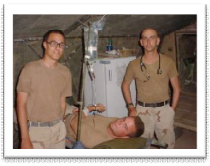
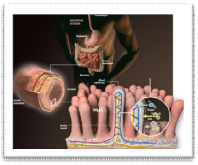

Infectious Diarrhea in Military Settings

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WRAIR Military Tropical Medicine Course 2011 08 Feb 2011

Outline

- Take Home Lessons
- Epidemiology of Infectious Diarrhea in the Military
- Causative Agents
- Clinical Presentation and Differential Diagnosis
- Diagnostic Considerations
- Treatment and Control

Take Home Lessons

- Acute diarrhea/dysentery in deployed military personnel (like travelers' diarrhea) is predominantly caused by bacterial enteropathogens
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- The U.S. military does not send its forces on overseas vacation
- Population-wide morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae

Definition of Travelers' Diarrhea

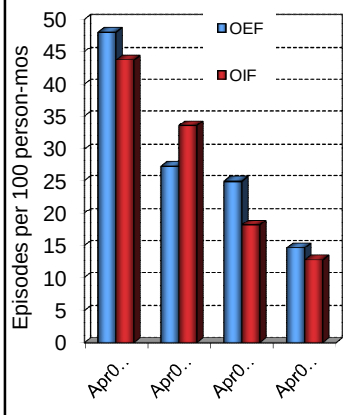
- Three or more unformed bowel movements occurring within a 24-hour period
- Often accompanied by other symptoms
  - cramps
  - nausea, vomiting
  - fever
  - blood in stools
- Typically acquired within first few weeks of travel/ deployment
- Ingestion of contaminated foods or less often drinks

Impact of Diarrheal Diseases in Modern Military Campaigns

- **World War II**: 'A few months of the year, malaria would cause more man-days lost, but on the calendar-year average, gastrointestinal infections were well ahead.'[1]
- **Vietnam War**: Diarrhea/dysentery largest single disease threat, leading to 4 times more hospitalizations than malaria[2]
- **OIF**: Acute enteric illness was leading cause of hospital admission among British forces during first 12 months of operations in Iraq[3]

(1) Ward TG: *History of Preventive Medicine*, US Army Forces in the Middle East, 19Oct41 - 23Jun44, Vol. 111. [Official record.]
(2) Wells RF, GI Diseases: Background and Buildup. In: Internal Medicine in Vietnam Vol II: General Medicine and ID, US Army Medical Dept 0:345-354.
(3) Grange, C: J Royal Army Medical Corps, 2005:151(2):101-104.

OEF/OIF, 2001-2007
Disease Burden 'By the Numbers'



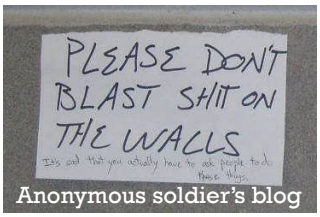
Cumulative deployments and disease burden

2,134,578	No. deployments ($\bar{x}$, 183 d)
145,871	No. deployments ($\bar{x}$, 19 d)
3,857,002	Cases of diarrhea
11,478,270	Diarrhea days
850,444	Ambulatory Medical Visits
17,356	Hospitalizations
1,114,208	Duty days lost
162,279	Liters of IV fluids infused

Force Health Impacts

Diarrhea with fever	9-25%
Dysentery	2-8%
Severe diarrhea	
Iraq	21-27%
Afghanistan	13-14%
Vomiting only	5-15%

clinical presentations



Anonymous soldier's blog

operational impact

↓ Job performance	45%
Confined to bedrest	13%
Hospitalized	2%
IV fluids	15-17%
Missed patrol	9-13%
Back-fill needed	12%
Grounded	6-12%
Fecal incontinence	32%

Clinical Infectious Diseases 2005

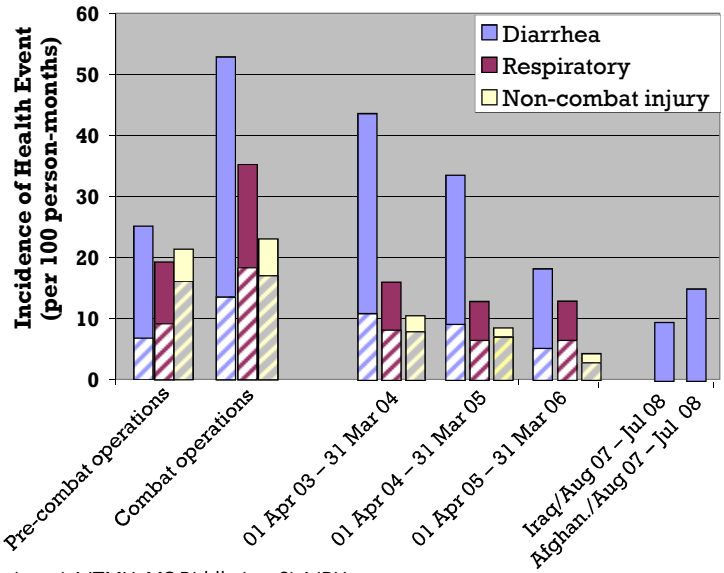
EDITORIAL COMMENTARY

I expect that our imaginations cannot fathom the problems attendant from the absolute urgency for relief from explosive vomiting and diarrhea when experienced within an armored vehicle under fire and at ambient temperature of > 40°C.

David O. Matson, MD

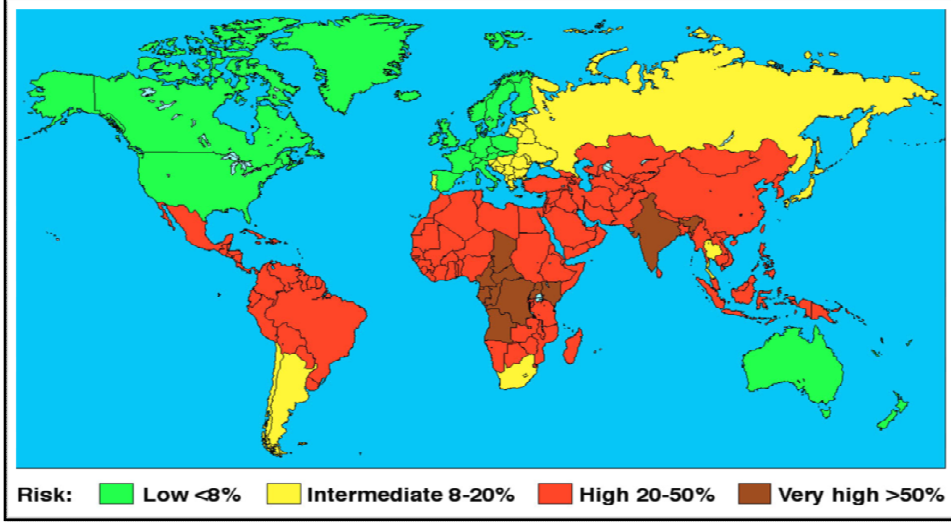
Infectious Diseases Section, Center for Pediatric Research, Norfolk, Virginia

Incidence of Illness based on Self-Reporting vs. DNBI

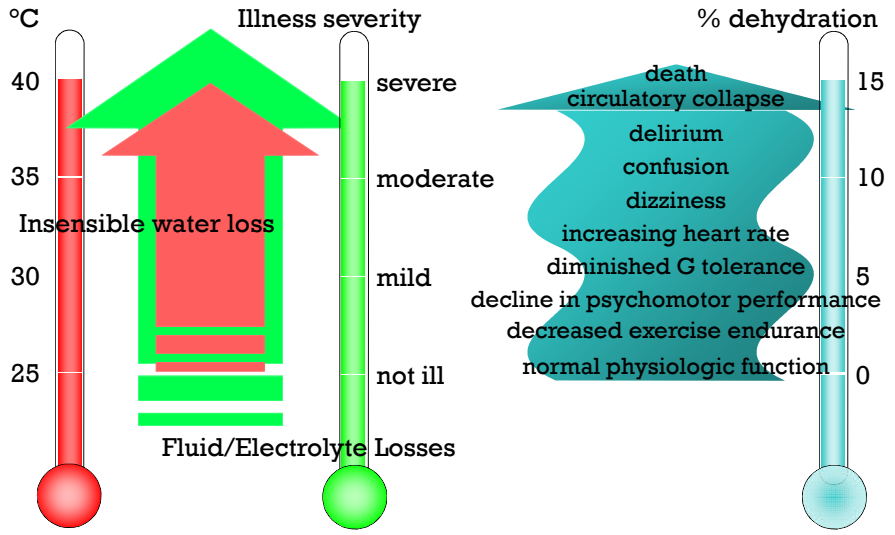


JW Sanders (2005) AJTMH; MS Riddle (2008) AJPH

Incidence Rates of Travelers' Diarrhea per 2-week Stay



Stressors in Extreme Conditions Amplify Diarrhea Morbidity



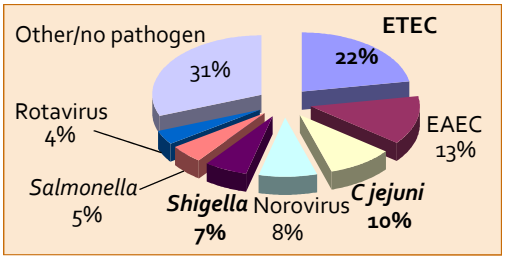
+ Causative Agents

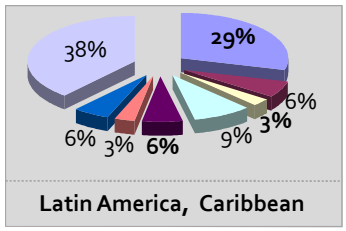
- Bacterial agents (80-90%)
- **Common**
  - Enterotoxigenic *E coli* (ETEC)
  - Enteroaggregative *E coli* (EAEC)
  - *Campylobacter*
  - *Shigella*
  - *Salmonella*
- **Less common**
  - Enteroinvasive *E coli* (EIEC)
  - *Aeromonas*
  - *Plesiomonas*
  - *Vibrio cholerae*

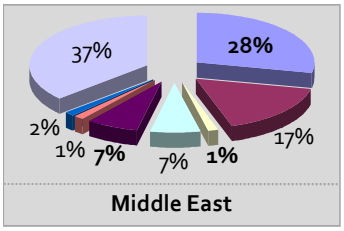
- Viral agents (5-10%)
  - Norovirus
  - Rotavirus
  - Astrovirus

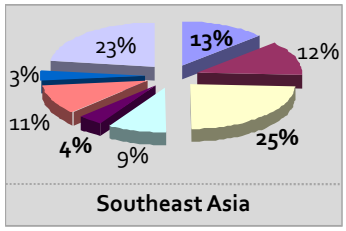
- Parasites (uncommon)
  - *Giardia lamblia*
  - *Cryptosporidium* spp.
  - *Cyclospora cayatanensis*
  - *Entamoeba histolytica*

Etiology of Diarrheal Diseases: *U.S. Military on Deployment*









MS Riddle et al. *Am. J. Trop. Med. Hyg.*, 74(5), 2006

Common Etiological Agents of Diarrhea in Iraq and Afghanistan

Study	Year	Area	Pathogens (top 3)	Comments
Thornton *et al* CID 2005	2003	Diwaniyah (South of Baghdad)	Norovirus 23% *Shigella* spp. 20% *Campylobacter* 4%	Sampling favored epidemics, diarrheagenic *E. coli* not assessed
Monteville *et al* AJTMH 2006	2004	Kuwait, Qatar, Iraq, Afghanistan	ETEC 32% EAEC 12% *Salmonella* spp. 6%	Case series out of TMC in Doha, Qatar
Sanders (unpublished)	2004	Anbar Province, Iraq	ETEC 23% EAEC 12% EIEC 7%	Systematic cross-sectional study
Faix (unpublished)	2005	Anbar Province, Iraq	*Salmonella* spp. 38% Cryptosporidium 38% ETEC 15%	Outbreak in food vendors run by FSNs

Clinical Presentations

- Watery diarrhea (80%)
  - ± Abdominal cramps
  - ± Nausea
  - ± Vomiting
  - ± Fecal urgency
  - ± Low-grade fever
- Dysentery (1-5%)
  - Fever
  - Tenesmus
  - Mucoid stools
  - Grossly bloody stools
- Acute gastroenteritis (≤10%)
  - Recurrent vomiting

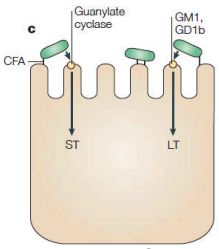
Clinico-pathological Considerations: Acute Travelers' Diarrhea

	Watery diarrhea	Dysentery	Gastroenteritis
Mechanism	Non-inflammatory (enterotoxin)	Inflammatory (invasion or cytotoxin)	Villus blunting (delayed gastric emptying)
Location	Proximal small bowel	Colon or distal small bowel	Small bowel
Usual Pathogens	All causative pathogens; most commonly ETEC, EAEC	*C. jejuni* *Shigella* spp. *Salmonella* (non-typhi) EIEC	Norovirus Rotavirus

Persistent Travelers' Diarrhea

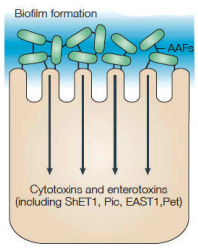
- Travelers' diarrhea is often self-limited, resolving in the majority of cases after several days
- Illness lasting >1 week: 10% of cases
- Illness lasting >1 month: 2% of cases
- Etiological considerations with persistent diarrhea
  - EAEC (occasionally, *Campylobacter*, *Salmonella*)
  - Parasitic diarrhea
    - *Giardia lamblia*
    - *Cryptosporidium parvum*
    - *Cyclospora cayatanensis*

Diarrheagenic *Escherichia coli* Common in Travelers: Pathogenesis



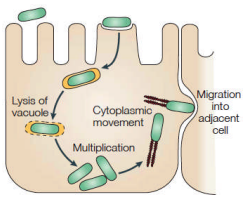
ETEC

- **Fimbrial colonization factors** mediate enterocyte adherence
- Elaboration of secretory heat-labile (LT), heat-stable (ST) **enterotoxins**



EAEC

- Enterocyte adherence and **biofilm formation**
- Elaboration of secretory enterotoxins and cytotoxins

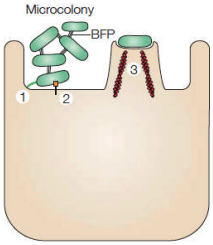


EIEC

- Colonic epithelial cell invasion
- Lysis of phagosome
- Cell-to-cell spread via actin microfilament nucleation

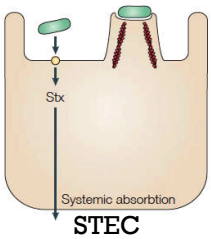
adapted from Kaper JB et al *Nat Rev Microbiol* 2004

Diarrheagenic *Escherichia coli* Uncommon in Travelers: Pathogenesis



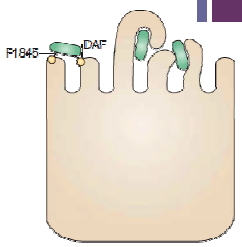
EPEC

- **Intimate adherence** to small bowel enterocytes
- **Attaching and effacing** lesion, with cytoskeletal derangement
- Induction of



STEC

- Induction of **attaching and effacing** (AE) lesions in the colonic epithelium
- Elaboration and absorption of **Shiga toxin** (STx)



DAEC

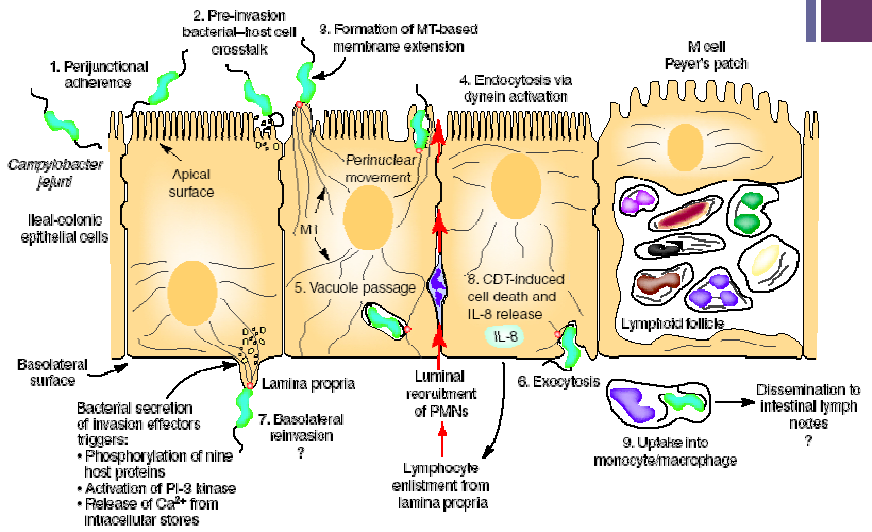
- Signal transduction effects
- Cellular projections induced that enwrap bacteria

adapted from Kaper JB et al *Nat Rev Microbiol* 2004

Enterotoxigenic *E. coli* (ETEC): Features

Transmission	foodborne (food, water)
inoculum size	High (≥ $5x10^6$ organisms)
populations at risk	infants, LDC; travelers to endemic regions
Estimated no. cases annually	200 million worldwide; > 500,000 under five death per year
typical clinical syndrome	watery diarrhea; dehydration in moderate-severe disease
phenotypic diversity	2 enterotoxins; > 20 fimbrial types
sequelae	physical and cognitive retardation; malnutrition

Campylobacter jejuni Pathogenesis

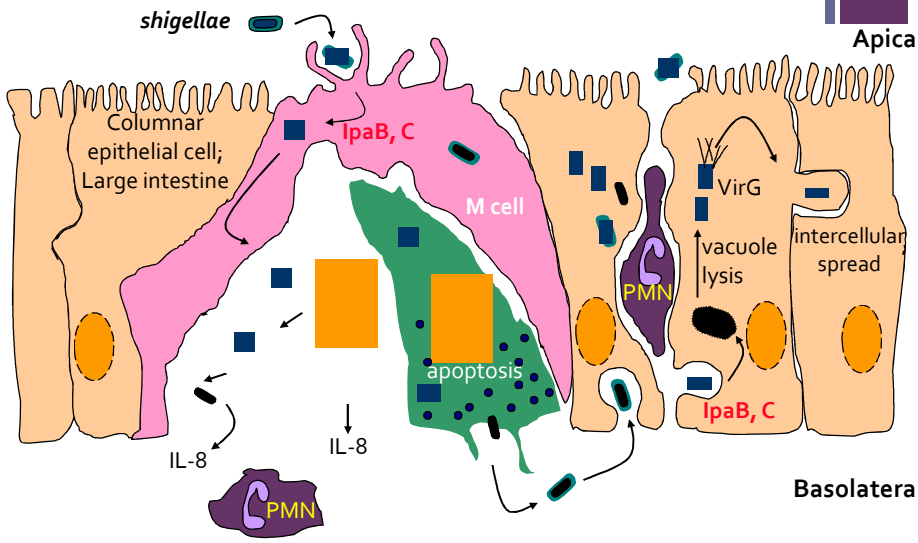


Kopecko DJ et al, Trends Microbiol 2001;9:389

Campylobacter jejuni: Features

Transmission	foodborne (food, water)
inoculum size	low (≥ $5x10^2$ organisms)
populations at risk	infants, LDC; travelers to hyperendemic regions; young people, HDC
geographic 'hotspots'	SE Asia, North Africa (Morocco)
typical clinical syndrome	acute inflammatory enteritis
serotypic diversity	multiple (108 Lior, 47 Penner serotypes)
sequelae	reactive arthritis; Guillain-Barré syndrome; irritable bowel syndrome

Shigella spp. Pathogenesis



Shigellosis: Features

transmission	person-to-person; foodborne (food, water)
inoculum size	low (10-200 organisms)
reservoirs	**humans** only
populations at high risk	toddlers living in and travelers to LDC; crowding, poor sanitation (e.g., day care, institutions)
serotypic diversity	Over 50 different serotypes (determinant, LPS)
key pathogenic processes	invasion, spread, inflammatory response; cytotoxicity (*S. dysenteriae* type 1, Shiga toxin)
typical clinical syndrome	**dysentery** (most commonly, acute watery diarrhea)
natural immunity	Medium-term, serotype-specific immunity
sequelae	Reiter's syndrome; reactive arthropathy; hemolytic uremic syndrome

LDC, less developed countries

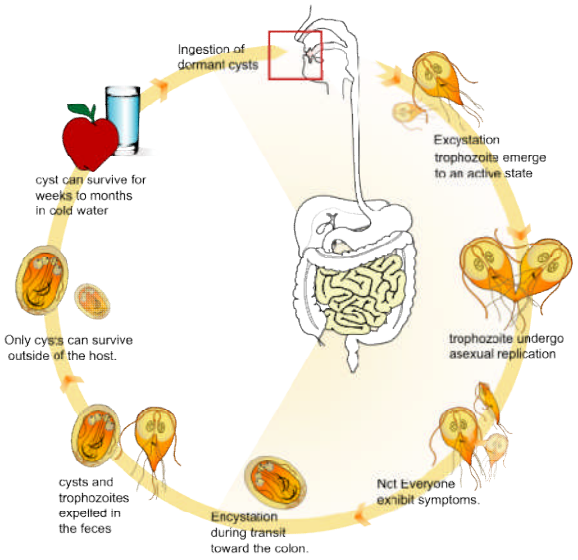
Differential Morbidity Associated with Major Bacterial Pathogens of Travelers' Diarrhea

Pathogen profile	ETEC	*C jejuni*	*Shigella*
Global prevalence (%)	22 (17-28)	10 (5-15)	7 (3-10)
Illness duration w/o treatment (mean, d)	3.6	8.0	7.1
Probability of causing incapacitation (%)	21-27	47	56-92
Illness duration after treatment (mean, d)	1.0	2.5	1.2

Noroviruses: Features

transmission	foodborne (food, water); person-to-person (crowding)
inoculum size	low (as few as 10 viral particles)
reservoirs	**humans** only; hardy virus, persists on fomites
populations at high risk	All age groups; outbreak potential in semi-closed populations – military populations, including ships
genotypic diversity	3 genogroups, and ≥ 25 genotypes
key pathogenic processes	Limited to small intestine, broadening/blunting of proximal intestinal villi; transient malabsorption
typical clinical syndrome	Sudden onset of vomiting and non-inflammatory diarrhea; duration typically ≤72 hours
natural immunity	Short-term homologous immunity; possible long-term immunity with repeated exposure
sequelae	No evidence of serious long-term sequelae

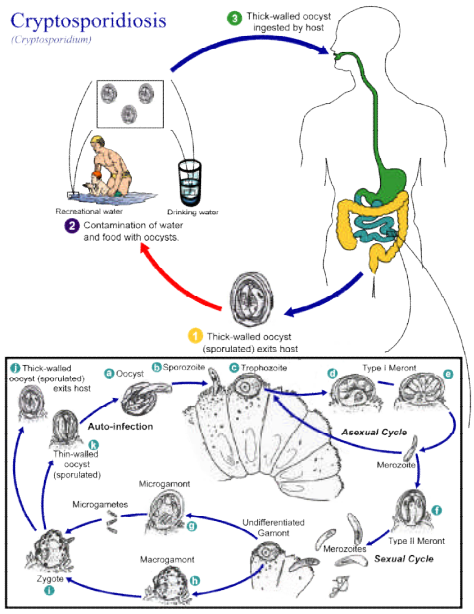
Giardiasis: *Life Cycle*



Giardiasis: Features

transmission	contaminated water; infected food handlers
inoculum size	low (as few as 10-25 cysts)
reservoirs	Humans and other mammals
populations at high risk	backpackers; young children LDC; higher risk with travel to Russia, Mexico, SE Asia, South America
antigenic variation	on-off switch of variant specific surface proteins (VSP)
key pathogenic processes	Attachment to intestinal epithelium via ventral disc; flagellar motility; VSP switching evades IgA
typical clinical syndrome	watery diarrhea; epigastric abdominal pain, bloating, malabsorption, nausea, vomiting, weight loss
natural immunity	both humoral and cell mediated immunity play a role in clearance; specific mechanisms poorly understood
sequelae	Functional gastrointestinal disorders (IBS)

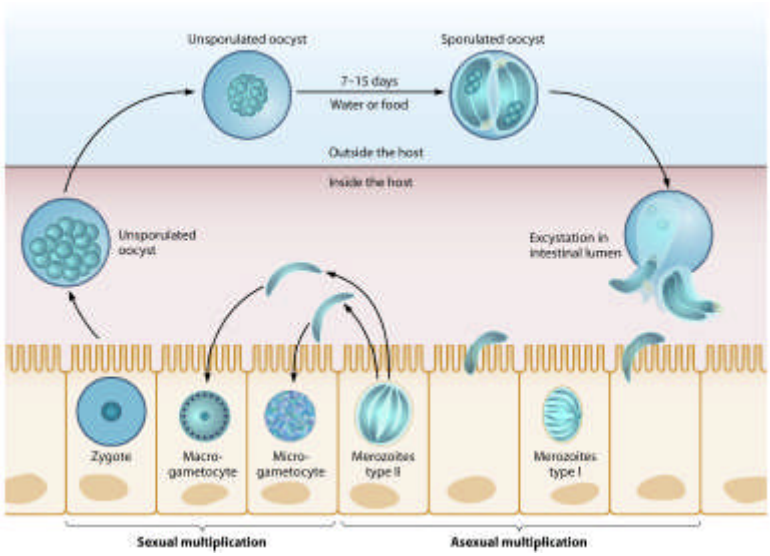
Cryptosporidium: *Life Cycle*



Cryptosporidium: Features

transmission	contaminated water and food; person-to-person
inoculum size	low (as few as 10 oocysts)
reservoirs	humans and other mammals (including livestock)
populations at high risk	HIV/AIDS; urban populations, municipal water contamination; children in LDC; travelers
species diversity	majority of human cases due to *C. hominis, C. parvum*
key pathogenic processes	Localizes in parasitophorous vacuoles in intestinal epithelium; distal small intestine; villous atrophy
typical clinical syndrome	watery diarrhea, abdominal cramps, vomiting, mild fever, and loss of appetite
natural immunity	Acquisition of natural immunity inferred from human challenge studies and age-related incidence in LDC
sequelae	intractable diarrhea in immunocompromised patients

Cyclosporiasis: *Life Cycle*



Cyclosporiasis: Features

transmission	contaminated food and water; no person-to-person
inoculum size	undefined
reservoirs	environmental; may be host species-specific types
populations at high risk	young children in LDC; travelers (especially Peru, Nepal, Haiti, Guatemala (*); immunocompromised
species diversity	*C. cayatanensis* found only in humans
key pathogenic processes	not well understood; localizes to small intestinal epithelium, partial villous atrophy, crypt hyperplasia
typical clinical syndrome	persistent diarrhea, anorexia, nausea/vomiting, abd cramps, flatulence, low grade fever, weight loss
natural immunity	decreased incidence with increasing age in high endemic areas of LDC;
sequelae	Chronic diarrhea in immunocompromised patients

Clinical and Diagnostic Evaluation

- Assess for dehydration
  - Mild (3-5%): dry mouth, decreased sweat and urine output
  - Moderate (6-9%): orthostasis, skin tenting, sunken eyes
  - Severe (>10%): hypotension, tachycardia, confusion, shock
- Consider setting of illness
  - Host factors
  - Environment, geographic region
  - Pathogen
- Define the clinical syndrome
  - Watery diarrhea
  - Dysentery
  - Gastroenteritis with recurrent vomiting
  - Persistent diarrhea

Considerations for Laboratory Work-up

- With military deployments, available laboratory capabilities may be austere
- Several common pathogens are not detectable with routine laboratory diagnostic tests
  - Diarrheagenic *E. coli* (ETEC, EAEC, EIEC)
  - Norovirus
- Differentiate inflammatory vs. non-inflammatory diarrhea
  - Clinical indicators of inflammatory disease include fever, tenesmus, visible blood in stool
  - Gross and microscopic examination of stool for blood and fecal leucocytes

Considerations for Laboratory Work-up

- Stool culture: clinical indications
  - Severe diarrhea (≥ 6 loose/liquid stools/24 hrs, incapacitating illness)
  - Febrile enteritis and/or dysentery
  - Persistent diarrhea (≥ 14 days duration)
  - Bloody diarrhea (at risk for Shigella, STEC)
  - Inflammatory enteritis (by stool diagnostics)
- Stool parasitology: clinical indications
  - Persistent diarrhea (≥ 14 days duration)
  - Diarrhea in traveler returning from known high risk region

Therapeutics: Water and Electrolyte Replacement

- Cornerstone of diarrhea treatment
- Military settings, insensible fluid losses increased with high ambient temperature, intense physical activity
- Oral rehydration
  - Physiological principle: Integrity of coupled transport of Na+ (plus H_2O and other electrolytes) with glucose or amino acids
  - Effective in majority of patients
- Intravenous rehydration
  - Severe dehydration
  - Altered sensorium
  - Intractable vomiting

Oral Rehydration Therapy

- Mild dehydration
  - Potable water or appropriate ORS
- Moderate-severe disease
  - ORS

	CHO g/L	Na mmol/L	CHO:Na	K mmol/L	OSM mOsm/kg
Rehydration Formulas					
WHO ORS	**13.5**	**75**	**1.2**	**20**	**245**
Pedialyte	25	45	3.1	20	250
Sports Drinks					
Gatorade	45	20	13	3	330
Powerade	60-80	~10	~6	~3	346-391
Other fluids					
Red Bull	108	35	~3	0	601
Apple Juice	690	3	230	32	694-773
Chicken Broth	0	250	-	8	500

Non-Antibiotic Therapy

- Consider with mild diarrhea for symptomatic relief
- Loperamide: antimotility agent of choice
  - Slows down peristalsis, intestinal transit
  - Increased fluid and salt absorption
  - 4 mg by mouth, then 2 mg after each liquid movement (up to 16 mg per day)
- Bismuth subsalicylate (Pepto Bismol)
  - Reduces number of passes stools
  - Does not limit duration of disease
  - 525 mg (2 tabs) every 30 min for 8 doses
  - Contraindicated in persons on salicylates, warfarin
  - Can interfere with doxycycline absorption (malaria prophylaxis)

Empiric Antibiotic Therapy

- Indicated for patients with moderate to severe diarrhea/dysentery
- Combination of antibiotic plus loperamide leads to rapid resolution of illness
- Re-evaluate patient if no improvement after 1 wk

Antibiotic (po)	Dosage (adult)	Considerations
Fluoroquinolones		
Norfloxacin	800 mg once or 400 mg bid	Re-evaluate 12-24 h after single dose. Continue for up to 3 d if diarrhea not resolved
Ciprofloxacin	750 mg once or 500 mg bid	
Ofloxacin	400 mg once or 200 mg bid	
Levofloxacin	500 mg once or 500 qd	
Azithromycin	1000 mg once or 500 mg bid x 3d	Use when *C. jejuni* suspected
Rifaximin	200 mg tid	Effective for non-invasive *E coli*

Increasing Fluoroquinolone Resistance among *Campylobacter* in Travelers

norfloxacin resistance rates

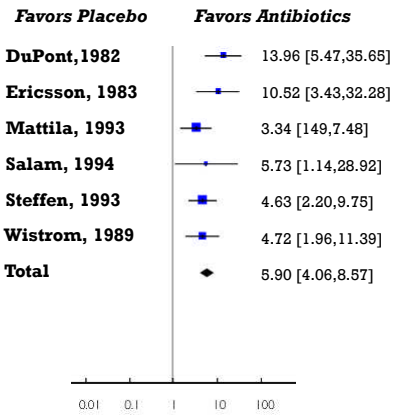
	1994-2000			2001-2006		
Region	No. isolates	No. resistant isolates	Resistance rate (%)	No. isolates	No. resistant isolates	Resistance rate (%)
Africa	162	22	13.6	114	36	31.6
Asia	208	74	35.6	95	67	70.5
Caribbean, Central & So. America	36	10	27.8	33	20	60.6

- Study site: Travel clinic, Antwerp, Belgium
- Erythromycin resistance showed modest increase over same period to 8.6% resistance in 2006

Vlieghe ER et al, *J Travel Med* 2008;15:419-25

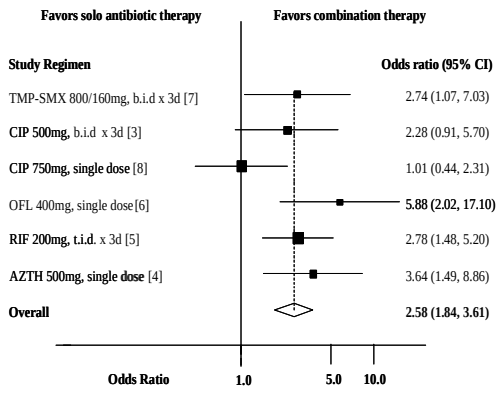
Effectiveness of Antibiotics, and Additive Effect of Loperamide)

Placebo vs antibiotics alone
(outcome: cure at 72 hours)
Bruyn G et al Cochrane Collab 2004



TLUS = 24 – 36 hours

Antibiotics alone or plus **loperamide**
(outcome: cure at 24 hours)
Riddle MS et al, CID 2008

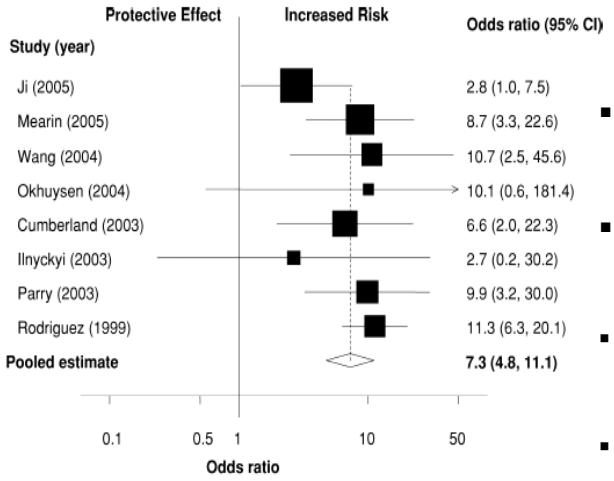


TLUS ~ 12 hours

Complications of Bacterial Diarrhea

Complication	Associated Bacterial Agents	Clinical Considerations
Dehydration	Any bacterial pathogen	Most important complication of watery diarrhea
Bacteremia	*Salmonella* spp., *C. fetus*	Certain conditions predispose to systemic *Salmonella* infection
Hemolytic-uremic syndrome (HUS)	STEC, *S. dysenteriae* type 1	Pathogenesis due to shiga toxin absorption and damage
Guillain-Barré syndrome	*Campylobacter jejuni*	40% cases of GBS caused by *C. jejuni;* molecular mimicry LOS
Reactive arthritis	*C. jejuni, Salmonella, S. flexneri*	Occurs in 2.1 per 100 000 *Campylobacter* infections
Irritable bowel syndrome	Most bacterial pathogens	≤ 10% incidence following bacterial enteric infection

Postinfectious Irritable Bowel Syndrome (PI-IBS)



- First described among British Forces during WWII **(Stewart. *Br Med J* 1950; 1(4650):405–9)**
- Approx. 1 in 12 people develop PI-IBS after infectious diarrhea
- Higher risk associated with prolonged illness and invasive pathogens
- Onset usually occurs within 6 months after infection
- Can persists 5-6 years in 60 - 70% of people

Halvorson *et al,* Am J Gastroenterol. *2006; 101:1894-9.*

+ Prevention of Enteric Diseases in Deployed Personnel

- Pre-deployment counseling of troops
  - Avoid exposure to pathogens transmitted by soiled food and drink ('boil it, cook it, peel it, or forget it!')
  - Seek early treatment with diarrhea
- Administer appropriate enteric vaccines
  - Typhoid vaccines (Ty21a [Vivotif]; Vi CPS [Typhim V])
  - Hepatitis A vaccine [Havrix, Avaxim]; Hepatitis B vaccine [Engerix-B]
- Antibiotic chemoprophylaxis
  - Not recommended for routine travel or deployment

Rifaximin and Chemoprophylaxis of Travelers' Diarrhea

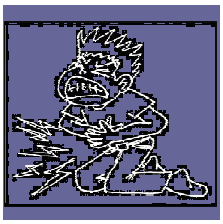
Pros	Cons

■ Poorly adsorbed oral antibiotic
  ■ Absent side effects
■ Low levels of rifaximin resistance among enteric pathogens
■ Prophylaxis against travelers' diarrhea for short-term travelers
  ■ ETEC predominant regions
  ■ ≥70% protection conferred
	■ Limited studies to date
	  ■ Geographically delimited
	  ■ Predominance of ETEC/EAEC
	  ■ Short duration travel
	■ Impact of widespread usage for prophylaxis unknown

Take Home Lessons

- Acute diarrhea/dysentery in deployed military personnel (like travelers' diarrhea) is predominantly caused by bacterial enteropathogens
- Treatment of moderate to severe illness with antibiotics should be the rule (not the exception)
- The U.S. military does not send its forces on overseas vacation
- Population-wide morbidity from acute illness is significant, and greatly compounded by growing evidence of associated post-infectious sequelae

Back-Up Slides



Comparison of Civilian Travelers vs. Deployed Military

Civilian Travelers	Deployed Military
Short-term trip (days-wks)	Long deployment (wks-mos)
Less crowding (cruise ship)	Crowded housing is norm
Leisure trips	Intensive work demand
Eating on economy	Availability of MREs
Varied exertion level	Typically high exertion
Typically poor access to medical facilities	Embedded medical assets
Self-treatment of diarrhea	Encourage early care seeking