



RED ALERT:
Blood in the Stools



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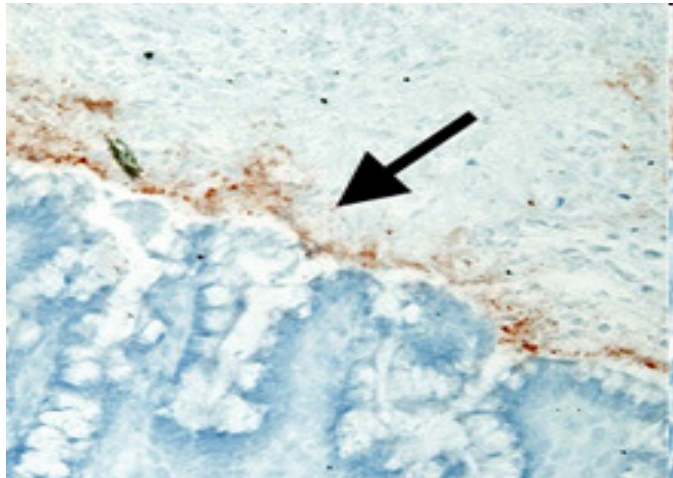


Bloody Diarrhea

- Any diarrheal episode in which loose or watery stools contain red visible blood
- Usually a sign of invasive enteric infection with pathogens that invade the bowel mucosa
- Indicates inflammation and tissue damage

Acute Dysentery

- Syndrome of bloody diarrhea with fever, abdominal cramps, tenesmus or painful defecation
- Implies **inflammatory colitis** or **invasion** and destruction of colonic mucosa by bacteria, cytotoxic products or parasites
- Pathologic changes:



superficial colonic lesions



deep submucosal ulcers

Epidemiology of Bloody Diarrhea

- Approximately 10-15% of diarrheal episodes in children < 5 yrs of age have visible blood in the stools
- Account for about 15-25% of diarrhea-associated deaths
- Compared with watery diarrhea, bloody diarrhea:
 - lasts longer
 - is associated with more complications
 - more likely to adversely affect a child's growth
 - has a higher case fatality rate

Acute Bloody Diarrhea in the Philippines



Age Group (yrs)	Number (Rate)*
< 1	887
1- 4	7052
5-14	875
15-49	1063
50-64	402
≥65	194
Total	10,463 (12.9)

*per 100,000



Non-Infectious Causes of Acute Dysentery & Inflammatory Enterocolitis

Specific Inflammatory Causes

- Idiopathic ulcerative colitis
- Crohn's disease
- Radiation enteritis
- Ischemic colitis

Anatomic disorders

- Diverticulitis
- Intussusception
- Malrotation & volvulus
- Juvenile polyps
- Mucosal prolapse syndrome

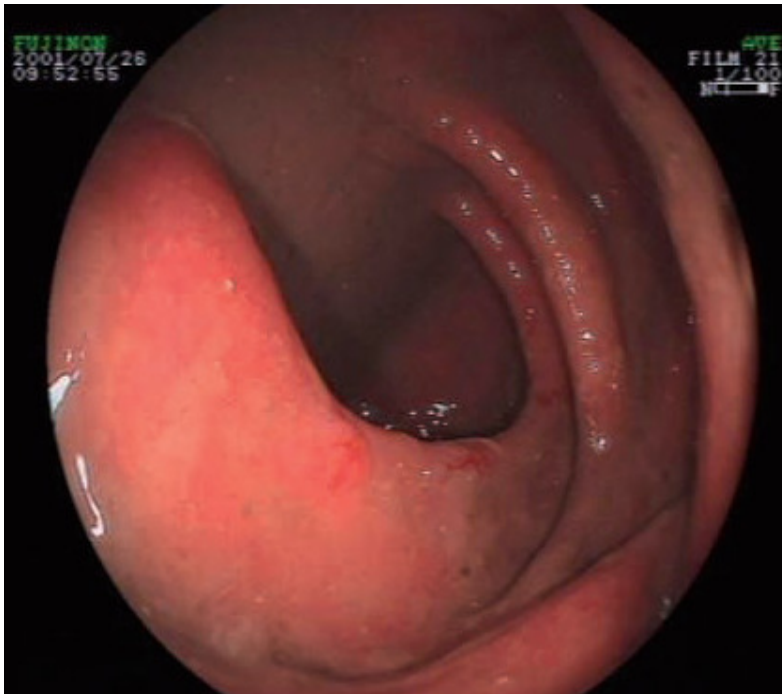
Immunologic causes

- Allergic enteritis:
 - Cow's milk colitis
 - Breast milk colitis
 - Nonspecific colitis
- Henoch-Schonlein purpura

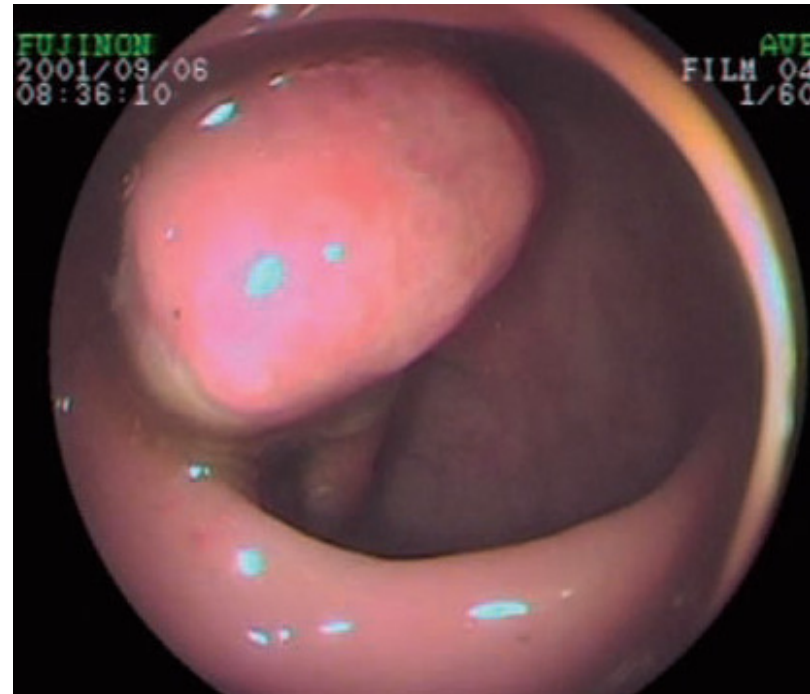
Hematologic problems

- Vitamin K deficiency

Non-Infectious Causes of Acute Dysentery & Inflammatory Enterocolitis



Ulcerative colitis resulting in mucosal inflammation



Juvenile pedunculated polyp in sigmoid colon

Infectious Causes of Acute Dysentery & Inflammatory Enterocolitis

Specific Infectious Processes

- Bacillary dysentery: *Shigella* spp.; invasive *E. coli*
- *Salmonella* spp: nontyphoidal salmonella; *S. typhi*
- *Campylobacter jejuni*
- *Yersinia enterocolitica*
- *Vibrio parahaemolyticus*
- *Entamoeba histolytica*
- *Balantidium coli*
- *Trichinella spiralis*
- *Spirillum* spp.

Proctitis

- *Neisseria gonorrhoea*
- *Herpes simplex*
- *Chlamydia trachomatis*
- *Treponema pallidum*

Other Syndromes

- Necrotizing enterocolitis
- Enteritis necroticans
- Pseudomembranous enterocolitis (*Clostridium difficile*)
- Typhlitis

Shigella

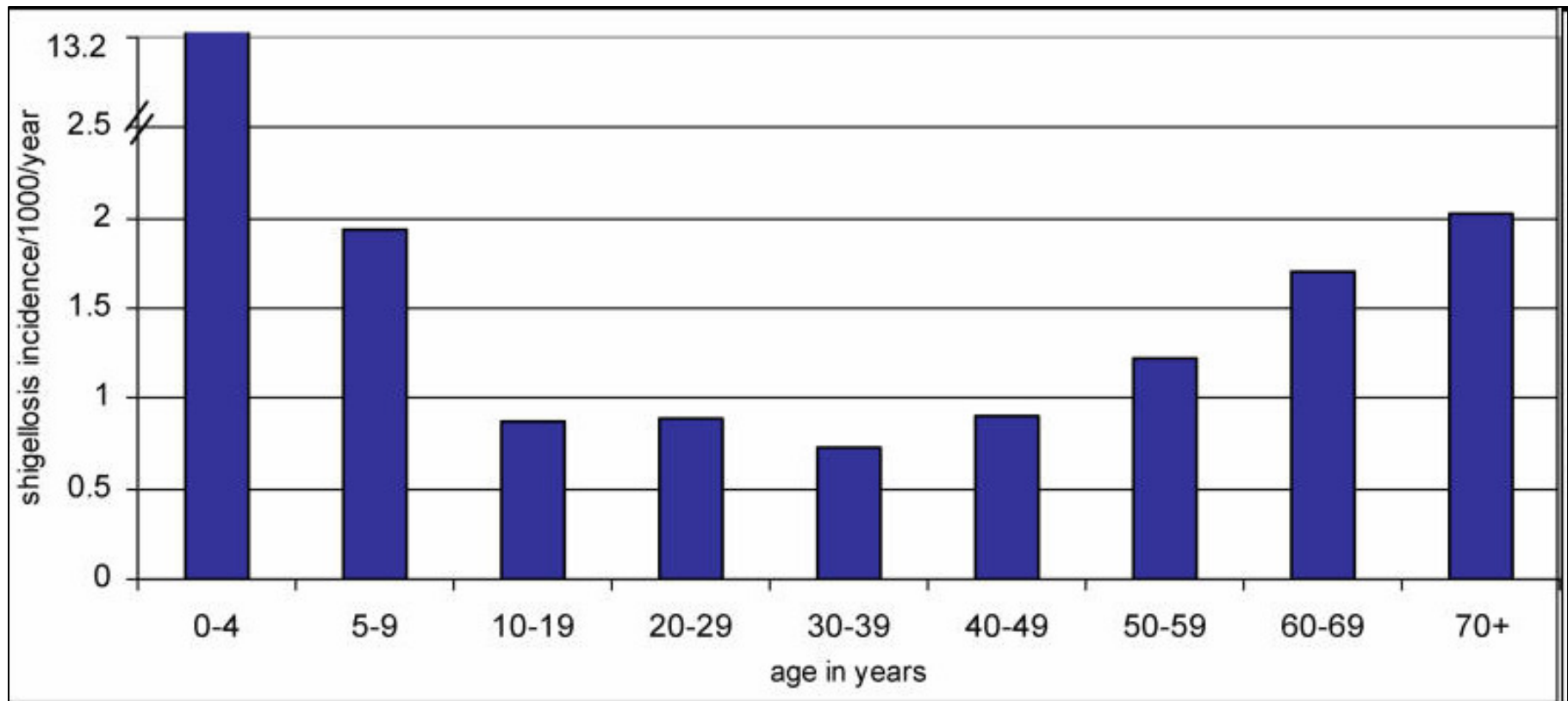


- Most common cause of bloody diarrhea in developing countries
- >200M infected; 650,000 deaths worldwide each year
- $\geq 50\%$ of all episodes occur in children under < 5 yrs old
 - ~370,000 deaths each year
- Highest incidence in densely populated areas with unsafe water supply & inadequate sanitation
- Transmitted by food or water contaminated with fecal material
- Commonly spread through contaminated hands; houseflies potential vectors



WHO. The management of bloody diarrhoea in young Children. WHO/CDD/94.49 WHO. Shigellosis: disease burden, epidemiology, and case management. Wkly Epidemiol Rec 2005:11

Overall Shigellosis Incidence by Age Group in Six Asian Countries* (2000-2004)



* Bangladesh, China, Pakistan, Indonesia, Vietnam & Thailand

Note: Shigellosis incidence 2.1/1000/y in all age groups;
Shigellosis incidence 13.2/1,000/y in 0–4 y age group.

Shigella



- Most common cause of bacillary dysentery
- Small gram negative bacilli, nonencapsulated & nonmotile
- Four serotypes:
 - *Shigella flexneri* - chief cause of endemic shigellosis
 - *Shigella dysenteriae* - causes both epidemic and endemic shigellosis
 - *Shigella sonnei* - least virulent
 - *Shigella boydii* - intermediate severity
- Virulence factors
 - LPS cell wall antigen
 - Shiga toxin – cytotoxic and neurotoxic



Shigellosis

- Incubation period usually < 72 hrs
- Variable severity of illness:
 - mild, self-limited watery diarrhea (~ 50%) → fulminant dysentery
- Rapid onset of watery stools that becomes bloody after 1-2 days
- Often accompanied by abdominal pain, fever, headache, anorexia
- Increased severity in infants <4 mo, malnourished, dehydrated, or recovering from measles
- Mortality 1-10%

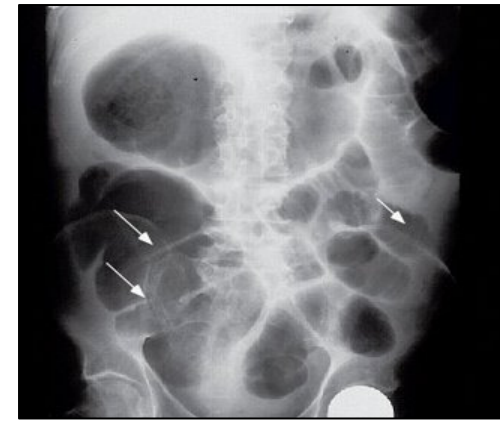


Risk factors for Death in Shigellosis

- Severely-malnourished Bangladeshi children with positive stool culture for *Shigella dysenteriae* type 1 or *S. flexneri* shigellosis
- Significant risk factors for mortality (multivariate regression analysis):
 - Altered consciousness (OR=2.6, 95% CI 1.0-6.8)
 - Hypoglycaemia, seGluc <3 mmol/L (OR=7.8, 95% CI 2.9-19.6)
 - Hypothermia T<36°C (OR=5.7, 95% CI 1.5-22.1)
 - Bronchopneumonia (OR=2.5, 95% CI 1.1-5.5)
- Early diagnosis of shigellosis AND proper management to prevent identified risk factors - likely to reduce *Shigella*-related mortality in severely malnourished children

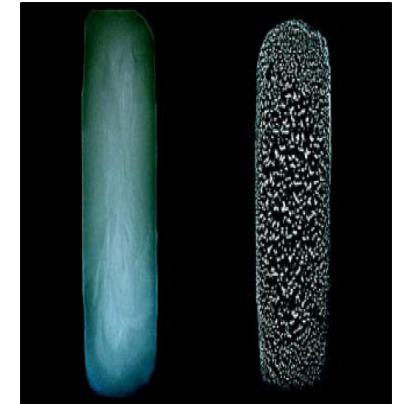
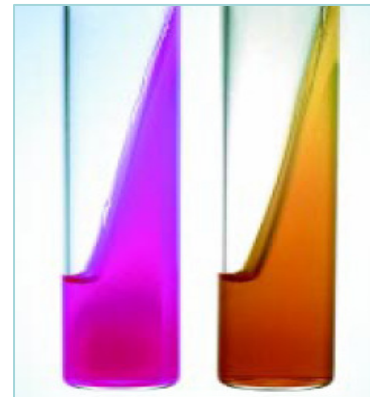
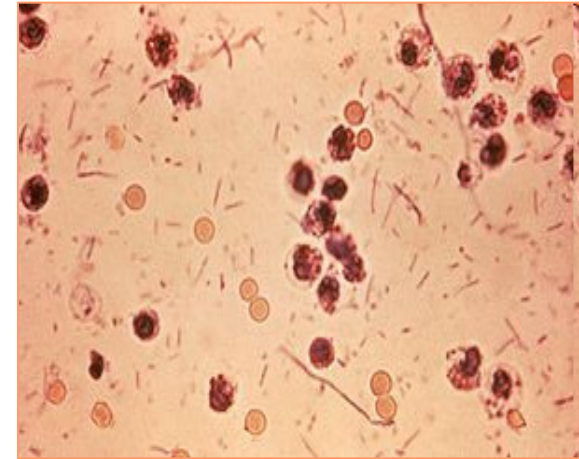
Complications of Shigellosis

- More frequent with delayed effective antibiotic treatment
 - rectal prolapse, toxic megacolon, bacteremia, persistent diarrhea, hyponatremia, hypoglycemia, hypoproteinemia,
- Hemolytic-uremic syndrome (HUS)
 - *S. dysenteriae* type 1 → Shiga toxin



Diagnosis of Shigella Dysentery

- Stool microscopy
 - Numerous PMNs, discrete RBCs; macrophages with ingested RBCs
- Stool culture
 - MacConkey agar
 - Xylose lysine desoxycholate agar (XLD), desoxycholate citrate agar
 - SS agar – may inhibit *S. dysenteriae* type 1 growth
 - Biochemical screening test and serological test (slide agglutination) for species identification
- Molecular-based tests
 - DNA probe hybridization
 - PCR - detect as few 10 cfu in stools



Antimicrobial Therapy of Shigellosis in Developing Countries

Drug	Cost & Availability	Resistant Organisms	Dose
Ampicillin	Inexpensive Widely available	Most <i>Shigella spp.</i>	Children: 25 mg/kg 4x a day x 5days Adults: 1g 4x a day x 5 days
TMP-SMX	Inexpensive Widely available	Many <i>S. dysenteriae</i> type 1; variable among other <i>Shigella spp.</i>	Children: 5 mg TMP & 25 mg SMX/kg 2x a day x 5 days; Adults: 160 mg TMP/800 mg SMX 2x a day x 5 days
Nalidixic acid	Inexpensive Moderately available	Increasing among <i>S. dysenteriae</i>; uncommon among other <i>Shigella spp.</i>	Children: 15 mg/kg 4x a day x 5 days; Adults: 1g 4x a day x 5 days

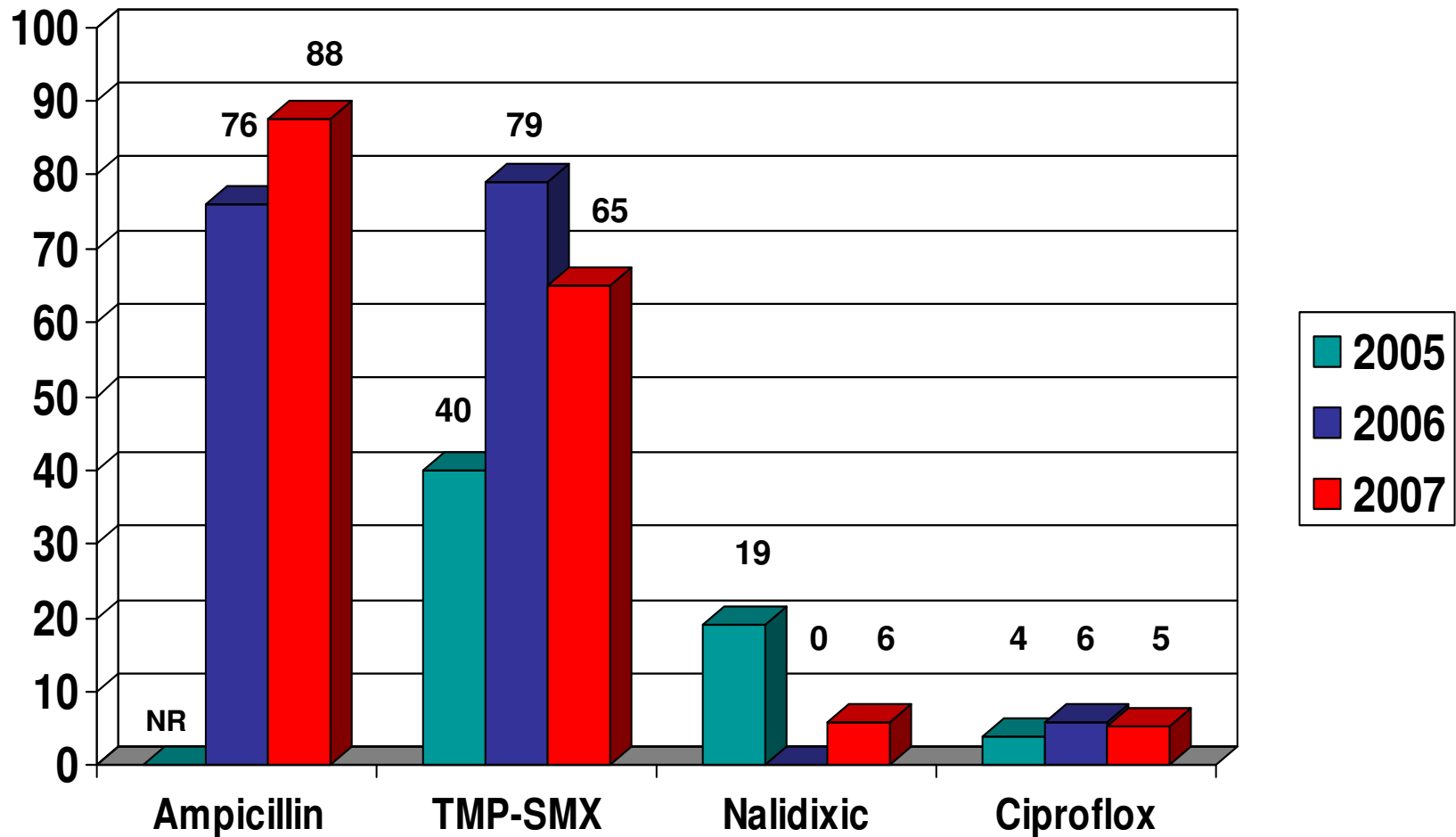
Antimicrobial Resistance Pattern for Four *Shigella* Species in 6 Asian Countries

Antibiotic	<i>S. flexneri</i> Serotypes (% of n)			<i>S. boydii</i> (% of n)	<i>S. dysenteriae</i> (% of n)	<i>S. sonnei</i> (% of n)
	2a (n = 527)	Other (n = 1,449)	Total (n = 1,976)	(n = 189)	(n = 110)	(n = 652)
Ampicillin	497 (94.3%)	1,156 (79.8%)	1,653 (83.7%)	46 (24.3%)	41 (37.3%)	64 (9.8%)
Cotrimoxazole	423 (80.3%)	1,067 (73.6%)	1,490 (75.4%)	91 (48.2%)	68 (61.8%)	603 (92.5%)
Nalidixic acid	172 (32.6%)	301 (20.7%)	473 (23.9%)	40 (21.2%)	9 (8.2%)	92 (14.1%)
Ciprofloxacin	11 (2.1%)	20 (1.4%)	31 (1.6%)	2 (1.1%)	0 (0%)	1 (0.2%)
Multidrug-resistant*	8 (1.5%)	10 (0.7%)	18 (0.9%)	0 (0%)	0 (0%)	0 (0%)

* Bangladesh, China, Pakistan, Indonesia, Vietnam & Thailand

Resistance of *Shigella* isolates to the first line drugs:
ampicillin 10-80%; cotrimoxazole 48-92%; nalidixic acid 8-24%

Percent Resistance of *Shigella spp.* DOH-ARSP 2005-2007



NR-not reported

Antimicrobial Therapy of Shigellosis in Developing Countries

Drug	Cost & Availability	Resistant Organisms	Dose
Ciprofloxacin	Expensive Moderately available	Rare among all <i>Shigella</i> spp.	Children: 10-15 mg/kg 2x a day x 3-5days; Adults: 500 mg 2x a day x 3-5 days
Pivmecillinam (Amdinocillin pivoxil)	Expensive Limited	Rare among all <i>Shigella</i> spp.	Children: 20 mg/kg 4x a day x 5days; Adults: 400 mg 4x a day x 5 days
Ceftriaxone	Expensive Moderately available	Rare among all <i>Shigella</i> spp.	Children: 20 mg/kg IV 2x a day x 5days; Adults: 1g IV once a day
Azithromycin	Expensive Moderately available	Rare among all <i>Shigella</i> spp.	Children: 10-20 mg/kg once a day x 5days; Adults: 1-1.5 g once a day x 5 days

FQ as First-line Treatment for Shigellosis

- Nalidixic acid – previously, back-up for treatment of *Shigella* resistant to ampicillin and cotrimoxazole; later became drug of choice
- Limitations of Nalidixic acid:
 - Increasingly ineffective in many parts of the world
 - failure to terminate fecal excretion of *Shigella*
 - may result in reduced susceptibility of *Shigella spp* to ciprofloxacin

The treatment of diarrhoea: a manual for physicians and other senior health workers. 4th ed. 2005. WHO/FCH/CAH/ 05.1; Technical updates of the guidelines on IMCI: evidence and recommendations for further adaptations. WHO 2005.

Efficacy Studies of FQ in Shigellosis in Children

Study	Age	No.	Regimen	Outcome
Lolekha 1991	6mo-13yrs	25	TMP/SMX 6mgT/kg/d q 12h x 5d	64% cure
		30	Nalidixic acid 5mg/kg/d q 6h x 5d	100% cure
		24	Norfloxacin 10-15mg/kg po q12hx5d	100% cure
Guyon 1994	8mo-13y	25	Pefloxacin 12 mg/kg once daily x 3d	100% cure; no relapse
		13	Pefloxacin 20 mg/kg single dose	
Bhattacharya 1997	8mo-10y	27	Nalidixic acid 60 mg/kg q6h x 5d	89% cure
		32	Norfloxacin 20 mg/kg po q12h x 5d	100% cure
Zimbabwe Dysentery Study Group 2002	1-12y	128	Ciprofloxacin 15 mg/kg po q 12h x 3d	100% bacteriologic cure for both, no relapse
		125	Ciprofloxacin 15 mg/kg po q 12h x 5d	

Ciprofloxacin Therapy for Invasive Diarrhea

- 201 children with invasive diarrhea, aged 0-11 mos
- Randomized to receive ciprofloxacin 10mg/kg BID or ceftriaxone 50 mg/kg IM once daily for 5 days
- Bacterial eradication rates in the ciprofloxacin-treated patients versus the ceftriaxone-treated group:
 - 100% versus 97% respectively for *Shigella* sp.
 - 73% versus 80% respectively for *Salmonella* sp.
 - 71% versus 83%, respectively for *Campylobacter* sp.
- Clinical cure or improvement was observed in 100% and 99% of the ciprofloxacin versus ceftriaxone groups, respectively
- Conclusion: no significant differences in clinical and bacteriological cure of ciprofloxacin and ceftriaxone

FQ as First-line Treatment for Shigellosis

- Advantages of Ciprofloxacin over Nalidixic acid:
 - Increased activity against Enterobacteriaceae
 - Less prone to selection of single-step spontaneous highly resistant organisms
 - Simplified treatment regimens (BID instead of 4x a day)
- Resistance to ciprofloxacin may develop when nalidixic acid is used
 - Nalidixic acid should no longer be used as first-line antibiotic to treat shigellosis, even in areas where it is still effective

Ciprofloxacin is now the preferred first line antibiotic for all patients with shigellosis, irrespective of age

Two Major Concerns on Use of FQ

- Safety
 - Both nalidixic acid and newer quinolones cause arthropathy in young animals
 - Potential cause of joint and bone toxicity in children
- Cost
 - Cost of treatment more expensive than the standard drugs
 - Reduced cost of ciprofloxacin with patent expiration

Safety of FQ in Children

- Bone or joint cartilage toxicity is an animal-specific issue not affecting humans (Burkhart 1997; Fukuda 1999)
- Retrospective Study – no joint-related adverse events at 45 days after treatment in 2030 children treated with ciprofloxacin for acute illness (Hampel 1997)
- Prospective studies
 - In children with CF treated with ciprofloxacin, no increased incidence of adverse musculoskeletal events documented by MRI (Williams 1998) or by histological studies (Schaad 1991; Pradhan 1995)
 - No clinical arthropathy or growth impairment among ciprofloxacin-treated neonates during a one year follow-up (Schaad 1994).
 - No quinolone associated arthropathy in children given gatifloxacin (Drossou-Agakidou 2004; Pichichero 2005).

Incidence of Tendon or Joint Disorders after FQ Use in Children

- Retrospective cohort study of records from United Healthcare Research database
- Compared incidence of joint disorders in 20,000 FQ treated children < 18 years old with 6,000 azithromycin treated children
- Results:
 - Incidence of joint disorders: 0.82% for ofloxacin and ciprofloxacin versus 0.78% for azithromycin
 - RR of joint disorders (compared with azithromycin): 1.04 [95% CI 0.72 to 1.51] for ciprofloxacin and 1.04 (95% CI 0.55 to 1.81) for ofloxacin
- Conclusion: Low risk of tendon and joint disorders (<1%) for FQ

Yee CL et al. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. *Pediatr Infect Dis J.* 2002; 21(6): 525–9.

Safety of FQ in Children

- Clinical trials have documented that FQ are safe and are as or more effective than standard therapy
- Incidence of adverse events is comparable to other antimicrobials
 - Common side effect of FQ: GI disturbance, CNS effects (e.g. headache, dizziness, sleep disorders, mood changes) and dermatological changes (e.g. rash, pruritus, pigmentation)
- Clinical data suggests minimal risk of joint toxicity in children and is outweighed by efficacy for life-threatening diseases like shigellosis
- FQ should never be used in pediatrics for routine treatment when alternative & effective antimicrobials are known & available

Antimicrobials Not Effective Against Shigella

- Metronidazole
- Streptomycin
- Tetracyclines
- Chloramphenicol
- Sulfonamides
- Nitrofurans (e.g. nitrofurantoin, furazolidone)
- Aminoglycosides (e.g. gentamicin, kanamycin)
- First and second generation cephalosporins (e.g., cephalexin, cefamandole)

Classification of *E. coli* Associated with Diarrhea

E. coli strain	Pathogenic Mechanism	Type of Diarrhea
Enteropathogenic (EPEC)	Small bowel adherence & effacement	Acute & chronic endemic & epidemic watery diarrhea
Enterotoxigenic (ETEC)	Small bowel adherence and effacement; HS/HL enterotoxin	Infantile diarrhea & traveler's diarrhea; watery
Enteraggregative (EAEC)	Small & large bowel adherence; enterotoxin & cytotoxin	Acute & chronic watery diarrhea, occasionally bloody
Enteroinvasive (EIEC)	Large bowel adherence, invasion & inflammation	nonbloody or bloody diarrhea
Enterohemorrhagic/ Shiga toxin producing (STEC)	Large bowel adherence & effacement; Shiga-like toxin	Hemorrhagic colitis; nonbloody or bloody diarrhea

Enteroinvasive *E. coli* (EIEC)



- Cause sporadic food-borne outbreaks in adults and children
- Transmission from food or water contaminated w/ human or animal feces or person-to-person from infected people or carriers
- Incubation period: 10 hrs to 6 days
- EIEC penetrate and multiply within colonic epithelial cells
- Symptoms of illness similar to shigellosis: febrile diarrhea, watery or bloody (dysentery)
- Diagnosis requires specialized techniques including serotyping, tissue culture, immunochemical test and DNA hybridization

Shiga toxin-producing *E. coli* (STEC)

- Includes Enterohemorrhagic *E. coli*
- Cause sporadic food-borne outbreaks from raw or undercooked ground meat, raw seed sprouts, unpasteurized milk, water or produce contaminated with bovine feces
- Incubation period: 1-8 days (ave 3-4 days)
- Shiga-like toxin responsible for edema, diffuse bleeding in the colon
- “Hamburger diarrhea” - initially nonbloody, progressing to bloody diarrhea, associated with abdominal pain & fever

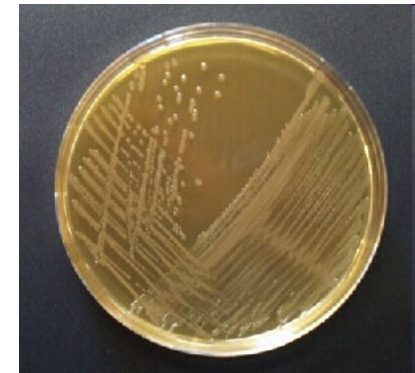


Shiga toxin-producing *E. coli*

- Shiga-like toxin - inhibit protein synthesis, damage epithelial cells, cause vascular necrosis and edema of intestinal tract (hemorrhagic colitis)
- Absorption and systemic complications:
 - Hemolytic-uremic syndrome (HUS)
 - Postdiarrheal thrombotic thrombocytopenic purpura (TTP)
- Type O157:H7 – most virulent; predominant cause of HUS and hemorrhagic colitis
- Other virulent serotypes: O26:H11; O103:H2, O111:NM; O121:H19; O145:NM
- Diagnosis confirmed by serotyping sorbitol-negative *E. coli* isolates or by using tissue culture or gene probes to detect cytotoxin

Diagnosis of *E. coli*

- Difficulty in diagnosis of infection caused by diarrhea-associated *E. coli*
 - most clinical laboratories cannot differentiate diarrhea-associated *E. coli* strains from stool flora *E. coli* strains
 - Intermittent excretion in stools
- Stool Culture:
 - Culture media: Sorbitol-MacConkey agar
 - Sorbitol positive - intestinal *E. coli* strains
 - Sorbitol-negative – STEC
- Serotyping for confirmation
- Serology
- Molecular-based methods: DNA probes, PCR



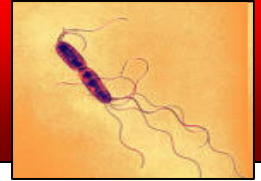
Hemolytic-Uremic Syndrome (HUS)

- Triad: Hemolytic anemia, thrombocytopenia, renal failure
- Develop within 2 weeks after onset of diarrhea
- More common in children < 4 yrs old
- HUS represents toxin-mediated endothelial cell injury resulting in altered vasculature and thrombi formation
- Etiology:
 - Common: *E. coli* O157:H7 (~5-10%); *S. dysenteriae* type 1
 - Less common: *Salmonella*, *Campylobacter*, *Bartonella*, viruses (e.g. coxsackie, ECHO, influenza, EBV)
- Management: dialysis; anticoagulants; plasmapheresis or FFP
- Prognosis: aggressive management of ARF ~ 90% recover renal function; 10-30% CRD; 3-5% mortality

Antimicrobial therapy for Bloody Diarrhea due to *E. coli*

- STEC – no increased benefit for treating with antibiotics; may increase risk for HUS due to ↑toxin
 - After antibiotic treatment, RR = 14.3 [95% CI 2.9-70.7] (Wong et al. NEJM 2000; 342:1930–6)
- EIEC - Antimicrobials for Shigella probably effective; ideally based on susceptibility testing
 - TMP-SMX
 - Azithromycin
 - Ciprofloxacin
 - 2nd or 3rd generation cephalosporins

Nontyphoid Salmonella

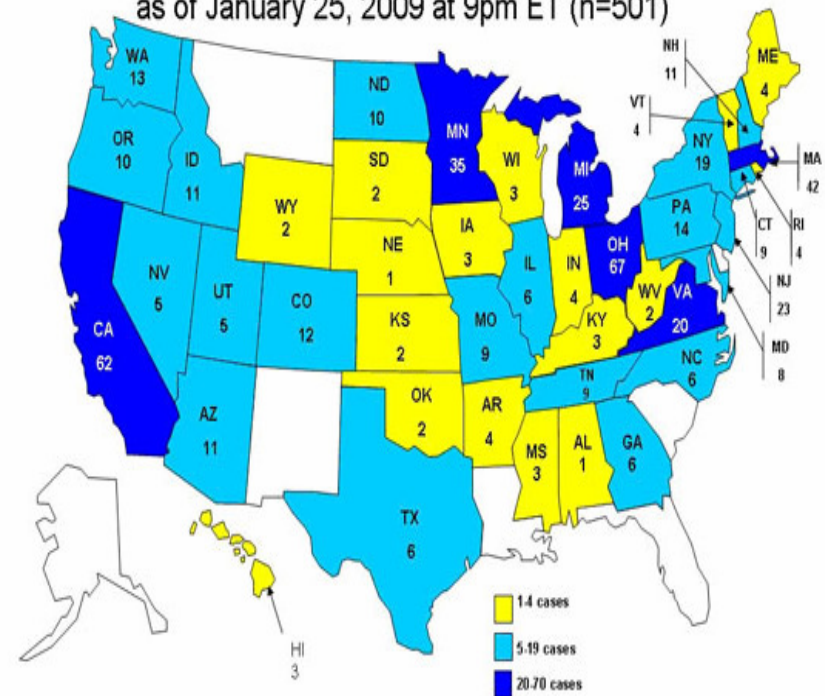


- Causes 1-5% of gastroenteritis in most developing countries
- Infection usually results from ingestion of undercooked poultry, contact with pets (reptiles)
- Incubation period 8-24 hrs after ingestion of infective dose; usually lasts 3-5 days
- Enterotoxin-mediated watery diarrhea; occasionally bloody
- Severe illness, bacteremia, and dissemination more likely in infants, elderly persons, those with impaired immune systems
- *S. typhimurium* - colitis with crypt abscesses, erosions and ulcerations of colonic mucosa resulting in bloody diarrhea

CDC Investigates 42-State Outbreak of *Salmonella typhimurium* Infections

- **January 25, 2009 Report:**
- 501 persons infected with the outbreak strain of *Salmonella typhimurium*, from 43 states.
- Patients range in age from <1 to 98 years; 22% hospitalized; 8 deaths
- King Nut (produced by Peanut Corporation of America, Georgia). peanut butter most likely source of bacteria causing the infections
- Recall of Austin and Keebler brand peanut butter crackers using peanut paste from the Peanut Corporation of America.
- Potential contamination of peanut butter containing products (such as cookies, crackers, cereal, candy and ice cream).

Cases infected with the outbreak strain of *Salmonella* Typhimurium, United States, by state, as of January 25, 2009 at 9pm ET (n=501)



Salmonella enterica ser. typhi



- Typhoid fever reported in 16-33 million cases, resulting in 500,000-600,000 deaths annually
- Highest incidence in children 5-19 years old and adults
- Transmitted by contaminated food and water
- Incubation period: 10-14 days
- Grossly bloody stools (10-20%) results from erosion of blood vessels in Peyer's patches
- Intestinal perforation and hemorrhage occurs in 2-3% - usually 2nd-4th wk of illness

Typhoid and Paratyphoid Fever By Age Group, Philippines



Age (yrs)	2002	2004	2006
<1	197	171	158
1-4	1613	1555	990
5-14	3771	3992	3005
15-49	5898	5111	4062
50-64	841	742	1005
≥65	335	240	372
TOTAL	13,664	12,535	11,374
Rate per 100,000	17.2	15.7	14.1



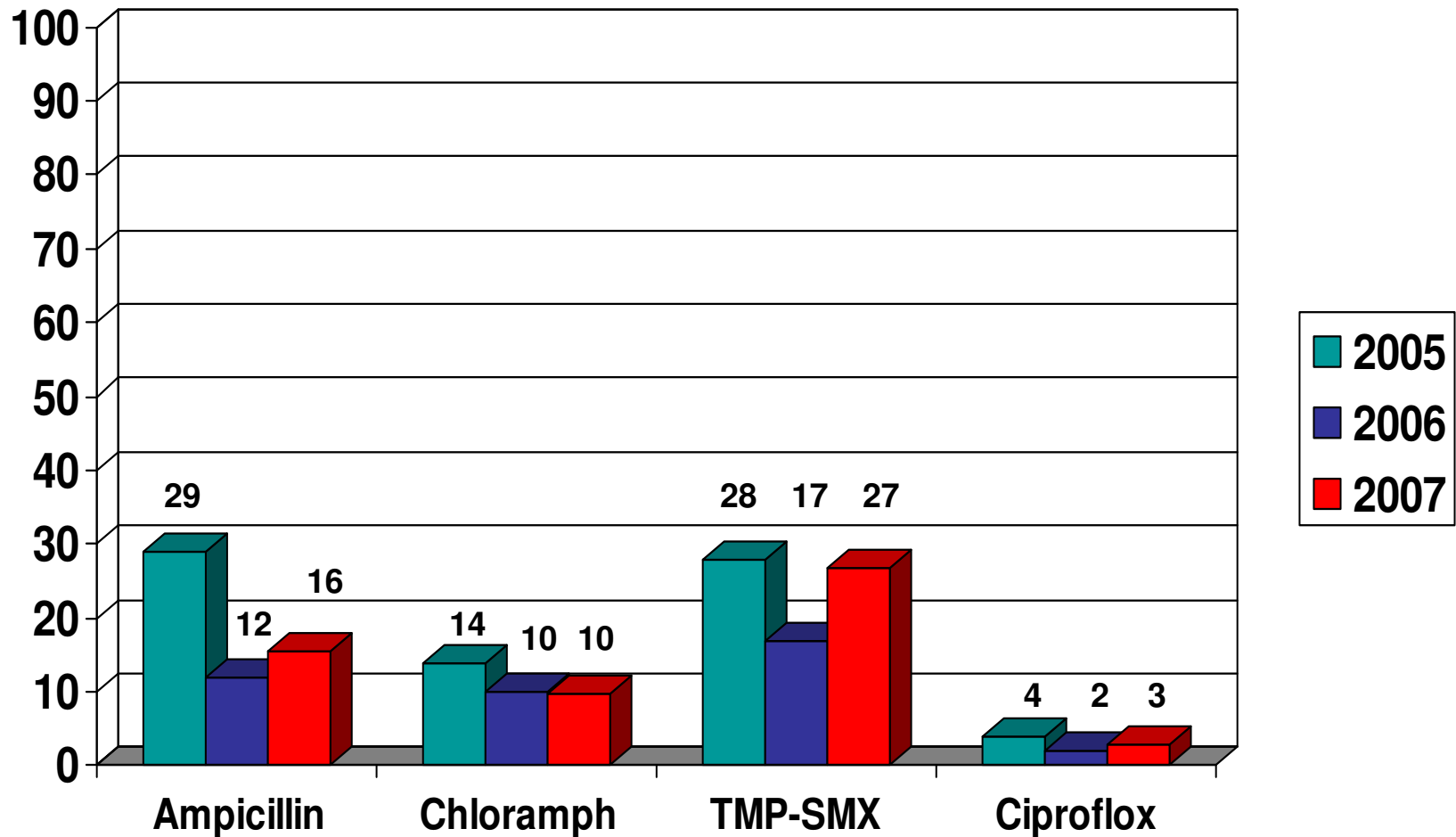
Diagnosis of Salmonella Infections

- Culture:
 - Stool, blood, bone marrow, urine
 - McConkey, Salmonella-Shigella agar, Bismuth sulfate agar
 - Serotyping to identify individual serotypes
- Serology: Particle agglutination slide tests, CIE, RIA, ELISA
- Molecular-based: DNA hybridization, PCR

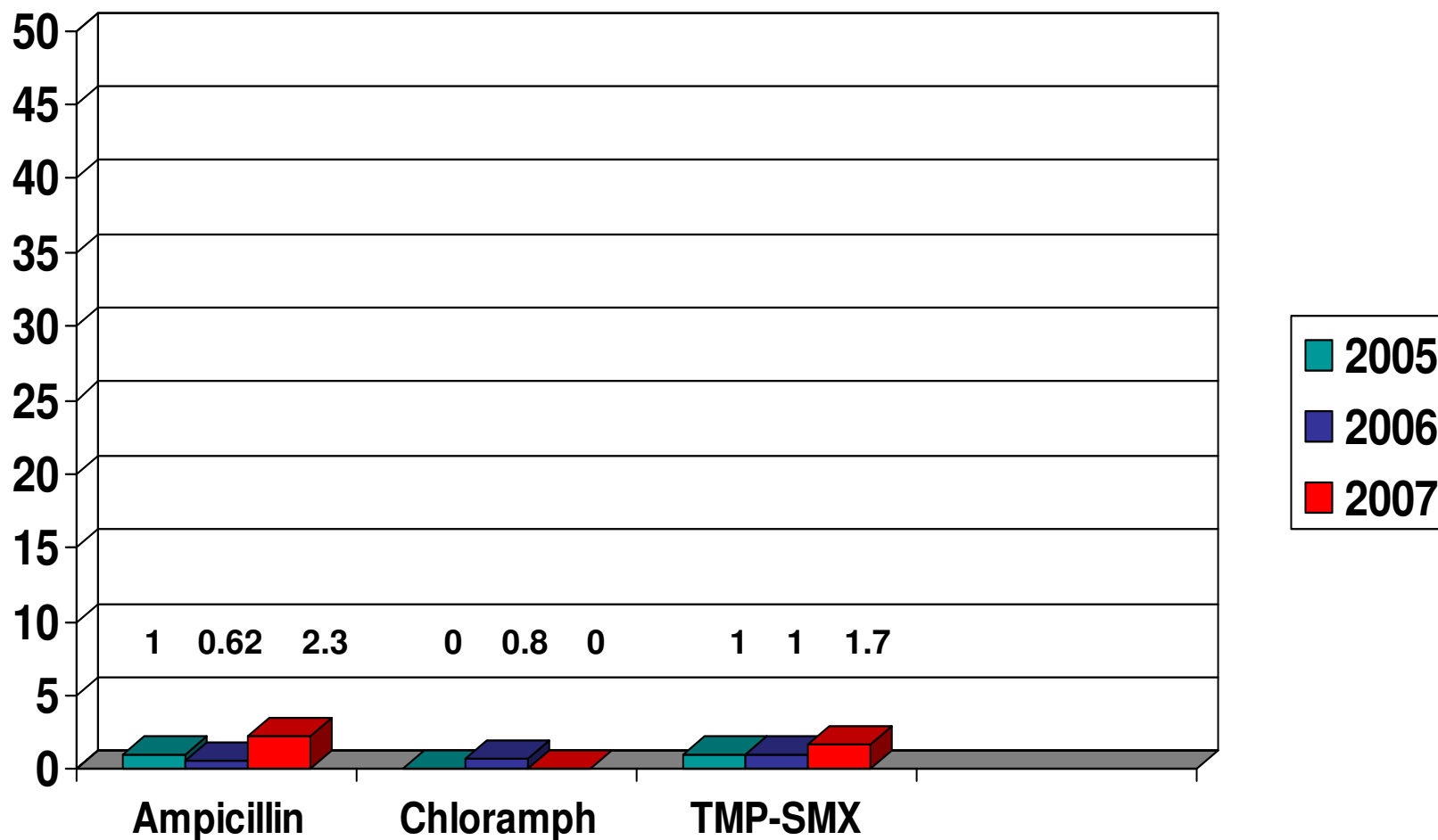
Antimicrobial Treatment of Non-typhoidal Salmonella

- Antibiotics not usually beneficial; may prolong bacterial carriage
S Sirinavin, P Garner. Antibiotics for treating salmonella gut infections. Cochrane Database of Systematic Reviews 1999 Issue 1. Art. No.: CD001167
 - No significant differences in length of illness, diarrhoea or fever between any antibiotic regimen and placebo.
 - Those receiving antibiotics had more frequent relapses (OR 4.84, 95%CI 2.91-8.05) and adverse drug reactions (OR 1.67, 95% CI 1.05- 2.67)
- Antibiotics indicated only in severe cases with invasive diarrhea and risk of septicemia:
 - < 3 mos of age or > 50 yrs
 - Impaired immunity: lymphoproliferative disease, cancer, uremia, taking corticosteroids
 - Patients with valvular heart disease, vascular grafts or artificial joints
 - Suspected bacteremia

Percent Resistance of Nontyphoidal *Salmonella* DOH-ARSP 2005-2007



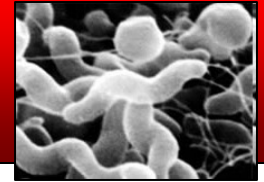
Percent Resistance of *S. typhi* DOH-ARSP 2005-2007



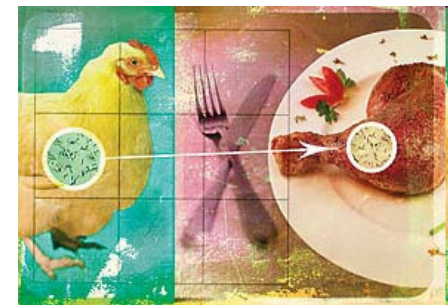
Antimicrobial Treatment of TF and Non-typhoid Salmonella Infections

- Susceptible Salmonella infections
 - Amoxicillin 100mg/kg/day (max 6g/day) x 14 days
 - TMP-SMX 8 mg T/kg/day in 2 divided doses x 14 days
 - Chloramphenicol 100mg/kg/day (max 4g/day) x 14 days
- Drug-resistant Salmonella
 - Third generation cephalosporins: ceftriaxone, cefoperazone, cefotaxime, cefixime
 - Fluoroquinolones: ciprofloxacin, ofloxacin
 - Azithromycin
 - Aztreonam
 - Carbapenems: Imipenem, meropenem

Campylobacter jejuni



- Causes 5-15% of diarrhea in infants worldwide
- Common in < 5 yrs old; most children acquire immunity during first year of life
- Estimated incidence: 400 million per year
- Pathogen frequently found in stools of healthy older children and animals
- Outbreaks associated with ingestion of uncooked meat or poultry, contaminated water, unpasteurized milk,
- Other sources of Campylobacter: infected pets (e.g. birds, cats, dogs, hamsters, turtles); streams, lakes, ponds, & dairy wastewater



Campylobacter jejuni



- Incubation period: 2-5 days
- Usually self-limited diarrheal illness (2-10 days)
- Cause severe watery diarrhea or frank dysentery with massive bleeding and toxic megacolon
- Gram-negative, nonspore-forming, motile, spiral or S-shaped rod with 1-2 flagella
- Pathology: direct invasion, cytotoxin & heat-labile enterotoxins
- Bacteremia and severe disease more common in immunocompromised; one in 1,000 cases of Campylobacter infection results in death
- Diagnosis:
 - Selective culture media: CampyBAP, Blaser or Skirrow's media; require special growth conditions (42°C incubation)
 - Darkfield with phase contrast exam of stools
 - Antigen detection by EIA
 - Molecular-based: DNA probes, PCR

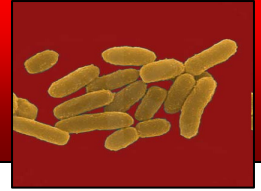
Postinfectious Complications of *Campylobacter* infection

- Reactive arthritis or Reiter's syndrome
 - Occurs in approx 2-7% of *Campylobacter* infections
 - affects large weight-bearing joints (knees, lower back)
 - persons who have HLA-B27 are genetically predisposed
- Guillain-Barre syndrome (GBS)
 - Reported in 1 per 1000-3000 *Campylobacter* infections
 - begins several weeks after the diarrheal illness
- Miller Fisher Syndrome (MFS)
 - neurological syndrome affecting nerves
 - Associated with ataxia, ophthalmoplegia, nonreactive pupils

Antimicrobials for *Campylobacter jejuni*

- Antimicrobials generally not required
 - Many asymptomatic by time diagnosis established and therefore do not require treatment
 - Antibiotic effective if given within first 3 days of illness
 - A meta-analysis of 11 RCTS showed decrease in duration of symptoms by 1.32 days and shortened excretion in stools (Ternhag A. Clin Infect Dis 2007;44: 696–700)
- Antimicrobials reserved for prolonged, severe symptoms or immunocompromised
 - **Children:** Erythromycin 10 mg/kg every 6 hrs for 5-7 days
 - **Adults:** Erythromycin 500mg every 6 hrs for 5-7 days
 - OR Ciprofloxacin 500 mg every 12 hrs for 5-7 days
 - OR Norfloxacin 400 mg every 12hrs for 3-5 days

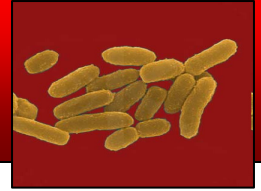
Yersinia enterocolitica



- Gram-negative bacteria found in birds, farm and domestic animals
- Epidemics related to contaminated water, milk & milk products
- Incubation period: 3-7 days
- Usually present with fever, abdominal pain, severe diarrhea
- Bloody diarrhea in 25-50% associated with necrosis of the Peyer's patches, chronic lymphadenopathy, and hepatic and splenic abscesses
- Infection may sometimes mimic appendicitis



Yersinia enterocolitica



- Pathology: diffuse ulcerations with necrosis and inflammation, numerous gram negative bacteria seen beneath mucosal ulcers and within microabscess in lymphoid tissue
- Diagnosis:
 - Selective culture media : Cefsulodin-irgasan-novobiocin agar plates
 - Serology: detection of antibody to Yersinia peaks 3-4 wks after onset of illness
 - PCR
- Antibiotics reserved for those with impaired immunity and extraintestinal spread
 - 3rd gen Cephalosporins \pm aminoglycoside
 - Alternative: fluoroquinolones; tetracycline

Vibrio parahaemolyticus



- Gram-negative, nonspore-forming, straight or curved rod with polar flagellum
- Incubation period: 9-25 hrs
- Explosive, watery diarrhea or full-blown dysentery
- Associated with ingestion of inadequately cooked fish or shellfish
- Usually self-limited illness lasting 3-4 days
- Bacteremia and extraintestinal spread may occur in immunocompromised

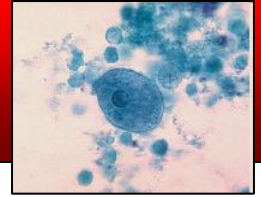


Vibrio parahaemolyticus

- Diagnosis:
 - Selective media:
 - TCBS agar
 - Wagatsuma medium
 - Immunoassays for detection of thermostable direct hemolysin (TDH)
 - Molecular-based: gene probe hybridization; PCR
- Supportive care only
- Antibiotics are recommended only in severe cases or in immunocompromised:
 - Tetracycline, cefotaxime
 - Fluroquinolones



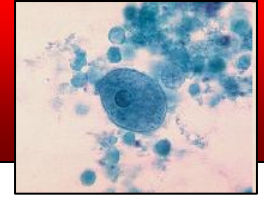
Entamoeba histolytica



- Amebiasis - a parasitic disease of worldwide public health importance
- Approximately 40 to 50 million people infected with *E. histolytica* develop amebic colitis or extraintestinal abscesses
- Invasive amebiasis results in up to 100,000 deaths per year
- Amebiasis is second to malaria in mortality due to protozoan parasites

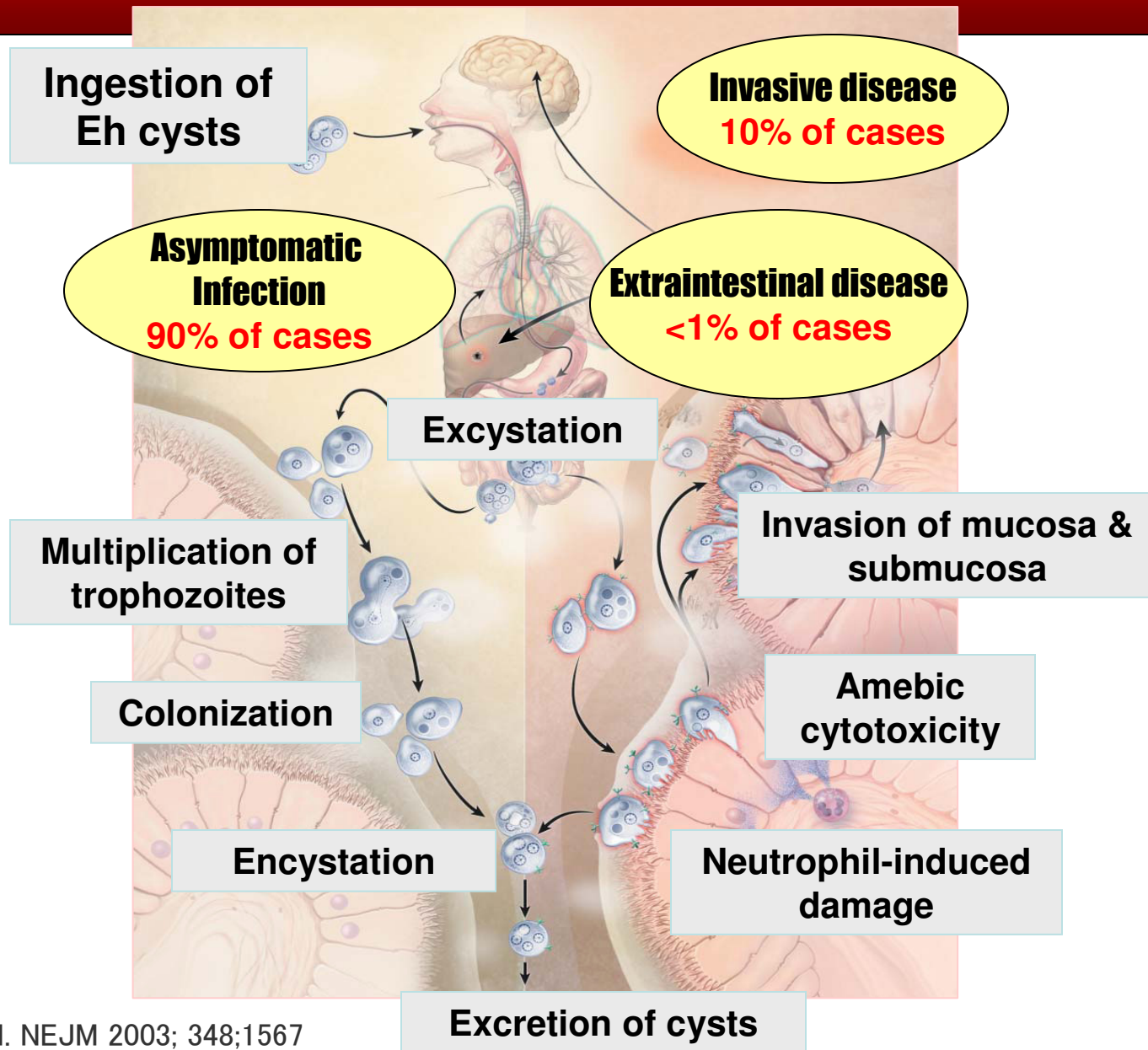
Walsh JA. Rev Infectious Dis 1986; 8(2): 228-38; WHO/PAHO/ UNESCO Wkly Epidemiol Record 1997; 72: 97-9; Li et al. Gastroenterology Clinics 1996; 25(3): 471-92; Petri WA et al. Parasit Today 2000; 16(8): 320-1.

Epidemiology of Amebiasis



- High rates of amebic infection in Asia, the sub-Saharan and tropical regions of Africa, Central and South America (Petri 1999)
- Seroprevalence rates of amebiasis in developing countries: 5% to 64%
- In the Philippines, variable prevalence rates depending on geographic area, study population, diagnostic method:
 - Stool microscopy: 0-8% (Cross 1980; Salazar 1990)
 - IHA: 1-13% (Cross 1980)
 - PCR: 0-65.5% (Rivera 1998; Rivera 2006)
- Infection commonly acquired by ingestion of food or water contaminated with *E. histolytica* cysts

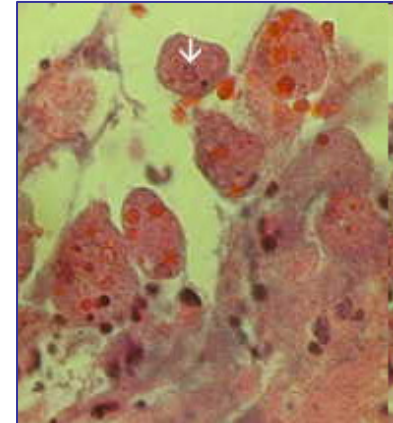
Life Cycle of *E. histolytica*



Clinical Forms of Amebic Colitis

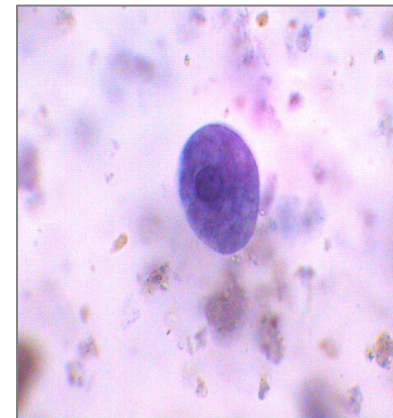
■ Amebic dysentery

- diarrhea with visible blood and mucus
- (+) *E. histolytica* trophozoites with ingested red blood cells (hematophagous trophozoite) in stools or tissues
- sigmoidoscopic examination: inflamed mucosa with or without discrete ulcers

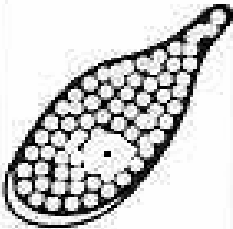

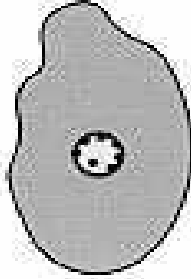

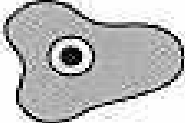
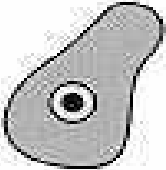
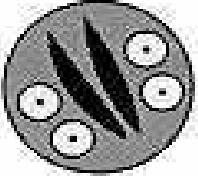
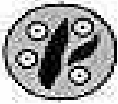
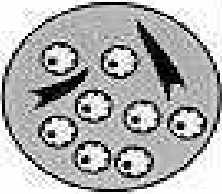


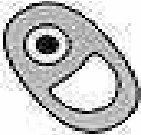


■ Nondysenteric amebic colitis

- recurrent bouts of diarrhea with or without mucus but no visible blood
- (+) *E. histolytica* cysts or trophozoites with no ingested red blood cells (nonhematophagous trophozoite) in stools
- sigmoidoscopic examination: normal



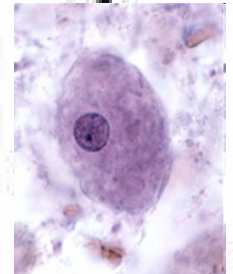
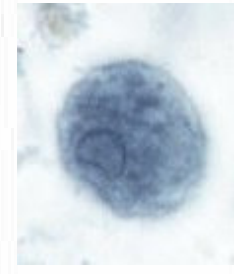
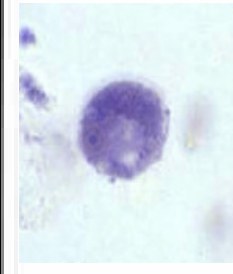
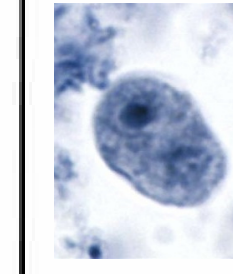

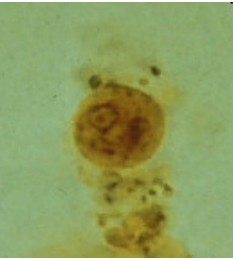
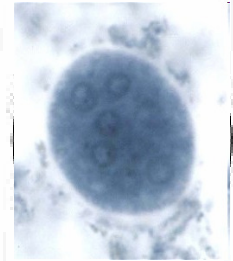
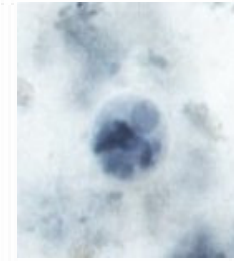
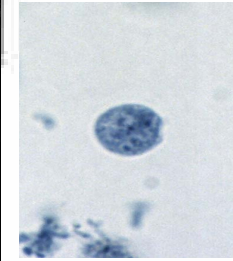
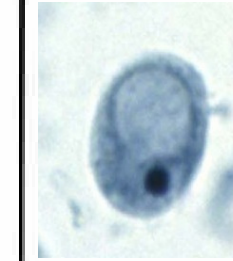


Structure of Human Ameba

Amebae						
	<i>Entamoeba histolytica</i>	<i>Entamoeba hartmanni</i>	<i>Entamoeba coli</i>	<i>Entamoeba polecki</i> *	<i>Endolimax nana</i>	<i>Iodamoeba bütschlii</i>
Trophozoite						
Cyst						

*Rare, probably of animal origin

Structure of Human Ameba

		Amebae					
		<i>E. histolytica</i> / <i>E. dispar</i>	<i>Entamoeba hartmanni</i>	<i>Entamoeba coli</i>	<i>Entamoeba polecki</i> *	<i>Endolimax nana</i>	<i>Iodamoeba bütschlii</i>
Trophozoite							
Cyst	 <small>© Don Lehman</small>						

*Rare, probably of animal origin

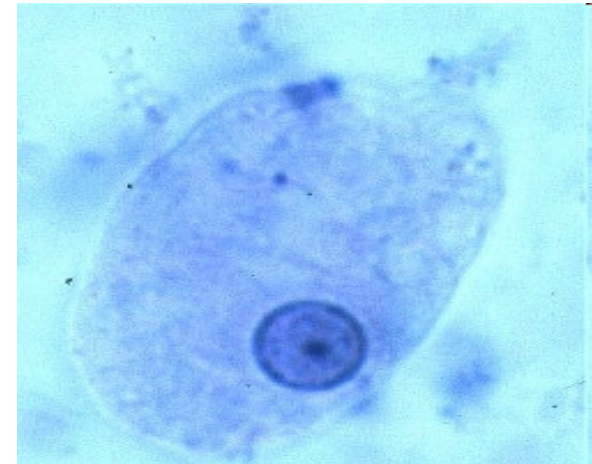
Hematophagous Trophozoite of *E. histolytica*



***E. histolytica* ingesting RBCs**

Diagnosis of Amebic dysentery

- Stool microscopy
 - Sn 25-60 (85-95 if (+) RBCs)
 - Sp 10-50%
- Amebic Stool Culture
 - Isoenzyme analysis or zymodeme demonstration to differentiate species
- Serology – Antibody tests
 - Sn 75-85%
 - Unable to differentiate acute and past infection
- Stool Antigen Detection tests
 - Sn 80-99%; SP 86-98%
- PCR
 - Sn 86-97%; Sp 72-99%



**E.histolytica/ E.dispar
trophozoite**



**E.histolytica/ E.dispar
cyst**

Drug Treatment of Amebic Colitis

- Tissue Amebicide – active against invasive forms in the tissues; inconsistent activity against cyst forms
 - Drug of Choice: Metronidazole 35-50mg/kg/day in 3 doses x 7-10 days
 - Alternative: Tinidazole 50 mg/kg/day (max 2 g) OD x 3 days
- Luminal agents - eradicate remaining cysts in the intestinal lumen; recommended after giving a tissue amebicide
 - Diloxanide furoate 20 mg/kg/day in 3 doses x 10 days
 - Paromomycin 25-35 mg/kg/day in 3 doses x 10 days
 - Iodoquinol 30-40 mg/kg/day in 3 doses x 20 days

Systematic Review on Amebic Dysentery

Dans L, Martinez E. *Clinical Evidence* 2006 June; 15: 1007-13)

- 12 RCTs: Tinidazole vs. metronidazole (9); Ornidazole vs placebo (1); Ornidazole vs. tinidazole (1); Secnidazole vs. ornidazole(1)
- General Findings:
 - Metronidazole increased failure rates compared to tinidazole (7/9 trials); fewer adverse effects with tinidazole 6 trials
 - Ornidazole had comparable failure rates compared to tinidazole and secnidazole
- Conclusion:
 - Likely to be beneficial: tinidazole, ornidazole and secnidazole
 - Unlikely to be beneficial: metronidazole
 - Unknown effectiveness: emetine, paromomycin

Meta-analysis on Antiamebic Drugs for Treating Amebic colitis

- 37 trials enrolling 4487 participants
- Tinidazole versus metronidazole:
 - Tinidazole reduced clinical failure by 72% compared with metronidazole (RR 0.28, 95% CI 0.15 to 0.51; 477 participants, 8 trials) and was associated with less adverse events
 - No evidence of advantage of tinidazole in eradicating *E. histolytica*
- Combination regimen versus Metronidazole alone
 - Combination therapy resulted in 64% fewer parasitological failures compared with metronidazole (RR 0.36, 95% CI 0.15 to 0.86; 720 participants, 3 trials)
 - Insufficient data to recommend which among the antiamebic drugs to use in combination to eradicate cysts and prevent relapse.
- Insufficient evidence for making conclusions regarding the efficacy of the other antiamebic drugs

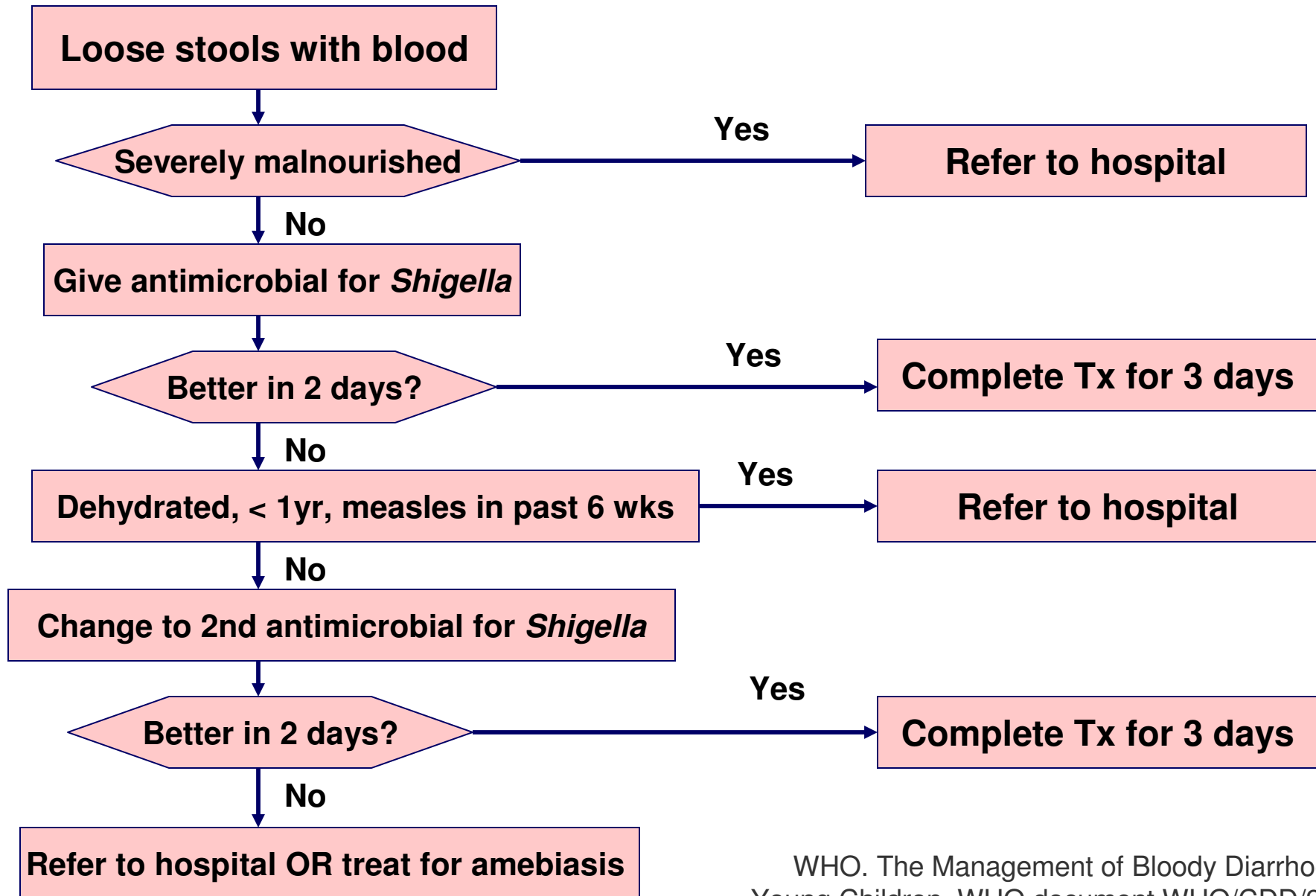
Meta-analysis on Antiamebic Drugs for Treating Amebic colitis

- The methodological quality of the trials was generally poor - not enough evidence to be certain about the results
- Diagnosis of amoebic colitis was based on stool microscopy - should be confirmed by a reliable test which differentiates *E. histolytica* from nonpathogenic amoeba
- Tinidazole is probably more effective than metronidazole in improving clinical symptoms and is as effective as metronidazole in eradicating *E. histolytica* in stools
- However, the choice of antiamebic drugs would depend largely on the availability and accessibility of drugs in the area.
- There is a need for more RCTs on efficacy of drugs for treating amoebic colitis with better methodological quality, using more accurate diagnostic tests and using standardized definitions for evaluating outcomes.

Four Principal Steps in the Management of Children with Bloody Diarrhea

- **F - Fluids**
 - Prevent dehydration with oral or IV rehydration fluids
- **F - Follow-up**
 - Re-evaluate clinical status after 48 hrs
- **F - Feeding**
 - Continue provision of nutritious food: breastfeeding; small frequent meals
- **A - Antimicrobial therapy**
 - Ideally, antimicrobial treatment should be based on suspected or identified specific bacterial pathogen

Outpatient Management of Bloody Diarrhea in Children < 5 yrs of age



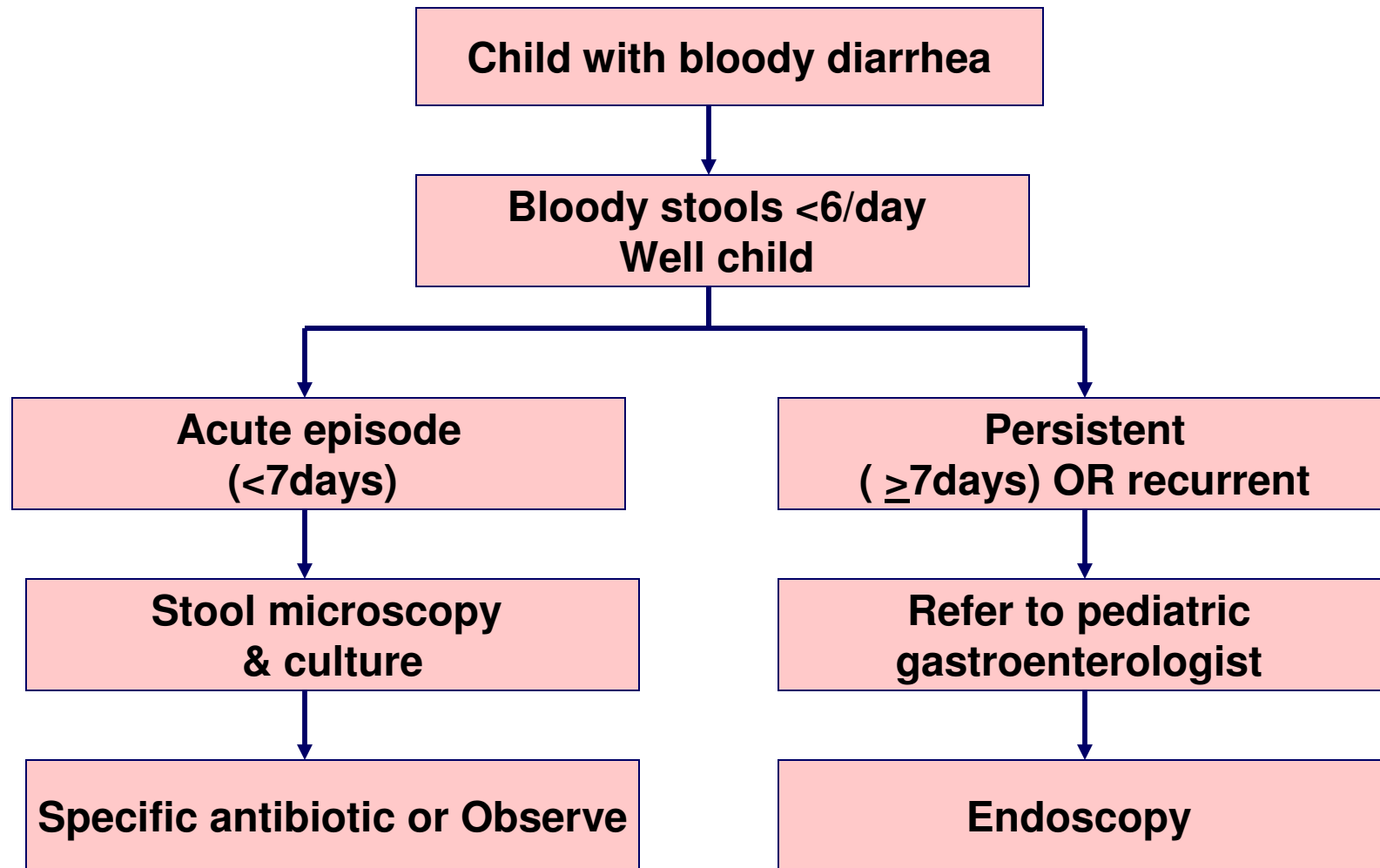
Antimicrobial Therapy of Bloody Diarrhea in Infants & Children

- Rationale for antimicrobial therapy against *Shigella*
 - *Shigella* is the most frequent cause of bloody diarrhea in this age group
 - Epidemics of bloody diarrhea are essentially caused by *Shigella dysenteriae* type 1
 - Shigellosis is more likely than other causes of diarrhea to result in complications and death
 - Early treatment of shigellosis with an effective antibiotic substantially reduces risk of severe morbidity

Metronidazole - NOT First-line drug for Bloody Diarrhea!

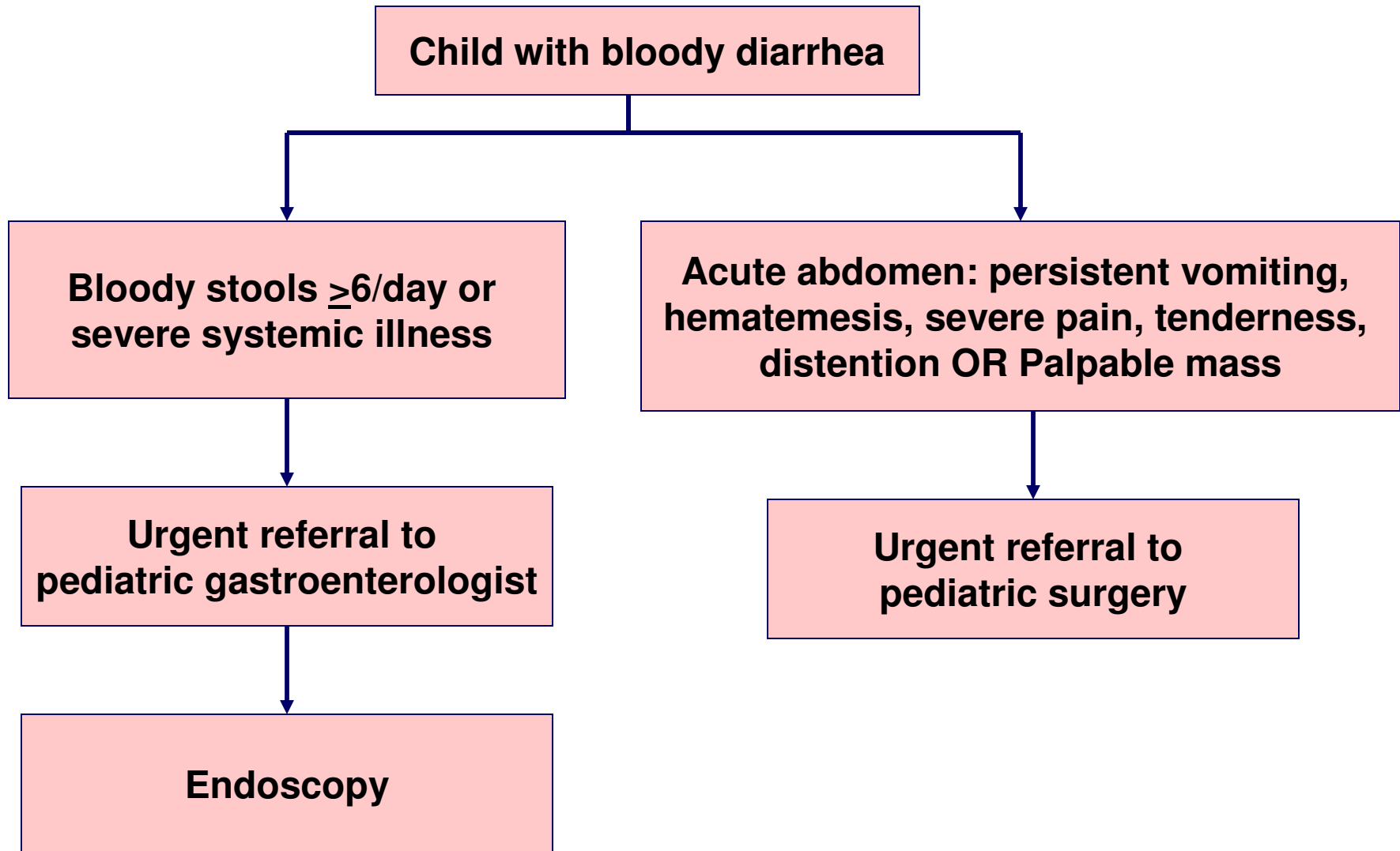
- Amebiasis is an *unusual* cause of bloody diarrhea in young children, usually causing less than 3% of episodes
- Young children with bloody diarrhea should not be treated routinely for amebiasis
- Metronidazole - no efficacy against *Shigella* or other invasive bacteria
- Anti-amebic treatment should be considered only when:
 - (+) trophozoites of *E. histolytica* containing red blood cells on stool microscopy done in a reliable laboratory
 - No clinical improvement after 2 different antimicrobials given for *Shigella*
 - Outbreak of amebiasis in the community

Algorithm for Initial Evaluation, Management, & Referral of Children with Bloody Diarrhea



Modified from Murphy M. Management of bloody diarrhoea in children in primary care. BMJ 2008;336:1010-5

Algorithm for Initial Evaluation, Management, & Referral of Children with Bloody Diarrhea



Modified from Murphy M. Management of bloody diarrhoea in children in primary care. BMJ 2008;336:1010-5

Adjunctive Drugs with Proven Efficacy for Bloody Diarrhea

- Zinc

- Zinc supplementation (10-20 mg/day) reduces number of stools, shortens the duration and severity of acute diarrhea, and reduces incidence of diarrhea for 2-3 months (Zinc Investigator's Collaborative Group. *Am J Clin Nutr* 2000;72:1516-22)
- Zinc reduced duration of shigellosis, shortened median time of disappearance of blood in stools, increased weight gain during recovery, and resulted in fewer episodes of diarrhea during the subsequent 6 months (Roy SK et al. *Eur J Clin Nutr* 2008 Jul; 62: 849-55)

Adjunctive drugs for Selected Causes of Bloody Diarrhea

- Steroids
 - Severe typhoid fever presenting with delirium, stupor, coma, shock
 - Steroids decrease mortality rate from 35-55% to 10% (Hoffman S et al. NEJM 1984;310:83-8; Punjabi N et al. PIDJ 1988;7:598-600)
 - Dose: Dexamethasone 3 mg/kg loading dose then 1mg/kg q 6hrs x 48hrs
 - Inflammatory bowel disease
 - Steroids and other anti-inflammatory drugs given during active disease flares (Murphy MS. BMJ 2008;336;1010-15)

Adjunctive Drugs with Unclear Benefit for Bloody Diarrhea

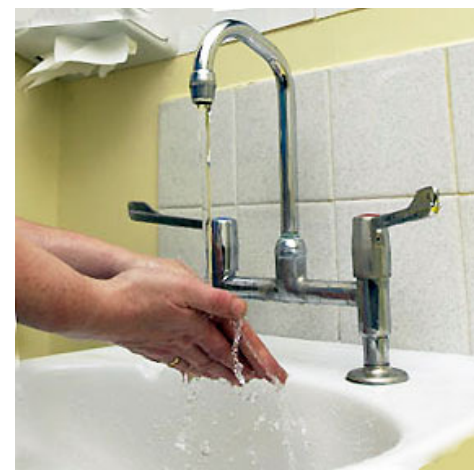
- Vitamin A
 - No significant effect of vitamin A on duration or severity of diarrhea (Bhandari 1997; Faruque AS 1999; Henning 1992; Khatun 2001)
 - Meta-analysis of 8 trials reported no effect of vitamin A on diarrhea-associated morbidity (overall RR = 1.00, 95% CI 0.94-1.07) (Grotto 2003)
 - Beneficial role of vitamin A for children with bloody diarrhea secondary to shigellosis remains unresolved (Hossain 1998; Salam 1999)
- Probiotics
 - Probiotics reduced the risk of diarrhea, mean duration and frequency of acute infectious diarrhea
 - Scarcity of data regarding effect of probiotics for specific infectious agents or for bloody diarrhea (Szajewska 2001; Van Niel 2002; Allen, B Okoko, E Martinez, G Gregorio, LF Dans. *Cochrane Database of Systematic Reviews* 2003, Issue 4)

Drugs which should NOT be given for Bloody Diarrhea

- Antimotility agents
 - Loperamide
 - Diphenoxylate and atropine (Lomotil)
- Antisecretory
 - Bismuth subsalicylate
- Adsorbents
 - Attapulgite
- Insufficient or no evidence of efficacy
- Ameliorate intestinal pain but delay clearance of pathogen and increase toxin production
- Associated with high rates of side effects: lethargy, ileus, respiratory depression, coma
- May increase development of HUS

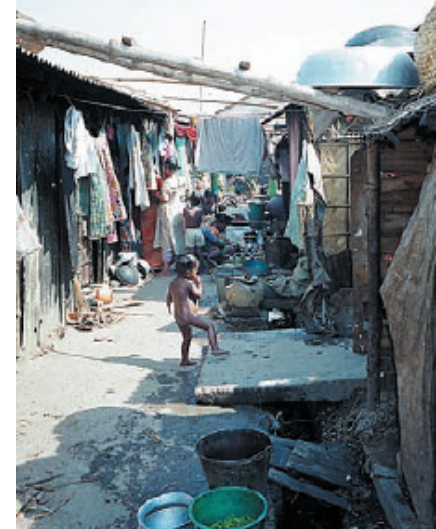
Control Measures

- Handwashing
- Contact Isolation
 - Until diarrhea resolves
 - Until post-treatment stool cultures negative for infecting organism



Public Health Measures to Prevent Transmission

- Provision of clean, safe drinking water
- Effective and sanitary disposal of human and animal waste
- Safe food preparation and food handling practices
- Education in basic personal hygiene and environmental sanitation



Summary

- Bloody diarrhea may be due to infectious or noninfectious causes
- Intestinal bacterial infection is the most common cause in children: Shigella, Salmonella, EIEC, STEC, Campylobacter and Yersinia
- Amebic dysentery diagnosed only when hematophagous *E. histolytica* trophozoites identified in the absence of more specific antigen tests or molecular-based techniques
- Fluid replacement - most important aspect of management
- Antibiotics are indicated only in selected cases, choice depends on identification of the infectious agent & its antimicrobial susceptibility pattern
- Non-infectious causes should be considered if no response to antimicrobial treatment
- Preventive strategies crucial to control infection and reduce transmission



**Thank
you**



1910

2010

UP MANILA-PGH DEPARTMENT OF PEDIATRICS

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in Quality Child Care*

Comparison of Different Diagnostic Tests for Amebiasis

Test	Specimen	Sensitivity (%)		Specificity (%)
		Amebic colitis	ALA	
Microscopy	Stool	25-60 (85-95 if (+) RBCs)	<10	10-50
	ALA fluid	NA	<25	100
Culture and Isoenzyme	Stool	50-70	<25	Gold standard
Antibody detection	IgM, acute	75-85	70-100	>85
	IgG, convales	>90	>90	-
Antigen Detection (ELISA)	Stool	>95	Usually (-)	>95
	Serum	65	75-100	>90
	ALA fluid	NA	100	90-100
PCR-based assays	Stool	>90	NA	>90
	ALA fluid	NA	100	90-100

Comparison of Different Diagnostic Tests for Amebiasis

Test	Time required	Technical expertise required	Cost	Remarks
Microscopy	1-2 h	Yes	Low	Widely used in developing countries
Culture and Isoenzyme	1-2 wks	Yes	High, labor intensive	Not for routine diagnostic procedure
Antibody detection	2-3 h	For certain antibody assays	Low	Limited use in endemic countries
Antigen Detection	3 h	None	Low	Potential for use in developing countries
PCR-based assays	1-2 days	Yes	High	DNA-based assays limited to research & clinical laboratories in industrialized countries

Amebicide Classes and Examples

Amebicide	Class	Example
Luminal	Arsenical compounds	Carbarsonne, acetarsonne or acetarsol, treparsol, diphetarsonne, glycobiarsonol or bismuth glycoarsanilate, stovarsol, thioarsenite
	Hydroxyquinoline derivatives	Chiniofon or quinoxyl, hydroxyquin, clioquinol or iodochlorhydroxyquin, iodoquinol or diiodohydroxyquin
	Dichloroacetamide derivatives	Diloxanide furoate or entamide furoate, clefamide or eticlordifene, quinfamide, etofamide
	Benzylamine derivatives	Teclozan, chlorbetamide or mantomide, chlorphenoxamide or mebinol
	Antibiotic amoebicides	Tetracycline, oxytetracycline, chlortetracycline, erythromycin, paromomycin, fumagillin
	Nitrothiazole salicylamide	Nitazoxanide

Amebicide Classes and Examples

Amebicide	Class	Example
Tissue	Emetine and its Derivatives	Emetine hydrochloride, emetine bismuth iodide, dehydroemetine dihydrochloride, dehydroemetine resinate
	4- Aminoquinoline	Chloroquine
	Thiazole derivative	Niridazole
	Nitroimidazole	Metronidazole, tinidazole, ornidazole, secnidazole, nimorazole

Antiamoebic Drugs for the Treatment of Amebic Colitis

- Two main classes of antiamoebic drugs:
 - Tissue amoebicides - active against invasive forms in the tissues; inconsistent activity against cyst forms
 - Luminal amoebicides – eradicate remaining cysts in the intestinal lumen
- Clinical trials show variable and inconsistent efficacy rates across studies; no single antiamoebic drug was reported to be better than the others
- Advantage of combination therapy: distinct activities of different drugs against the cysts and trophozoites found in the different sites
- Conflicting results on efficacy of:
 - Combination drug therapy compared to single drug
 - Single dose compared to multiple dose

Vaccines

- Available Vaccines
 - Typhoid fever vaccine
 - Ty21a oral vaccine- cumulative efficacy for 2.5-3yrs = 48%(95% CI 34-58%)
 - Typhoid Vi parenteral vaccine- 3 yr cumulative efficacy = 55% (95%CI 30-70%)
 - Conjugate Vi vaccine – 3.8 yr cumulative efficacy = 89% (95%CI 76-97%); most promising but unlicensed at this time

- Vaccines under development
 - Shigella vaccine - live oral and subunit parenteral vaccine candidates
 - Campylobacter vaccine – killed oral vaccine

Measures to Prevent Diarrhea in Infants

- Measures of proven efficacy:
 - Give only breast milk for the first 4-6 months of life
 - Avoiding the use of infant feeding bottles
 - Improving practices related to the preparation and storage of weaning foods (to minimize microbial contamination and growth);
 - Use clean water for drinking
 - Handwashing
 - Safe disposal of infant feces

Diagnostic Tests for Acute Dysentery

- Stool microscopy - useful preliminary test
 - (+) PMNs – indicates inflammatory process
 - (+) trophozoites or cysts
 - (+) parasites
- Stool culture - for all cases of bloody diarrhea
 - Detection of specific bacterial agent
 - Routine stool culture are limited to screening for *Salmonella* and *Shigella* species, and *Campylobacter jejuni*
 - May require special culture media, transport media, or incubation conditions, e.g. *Vibrio* and *Yersinia* species, *Escherichia coli* O157:H7, and *Campylobacter* species

Proper Collection of Stool Specimens

- Rectal swab
 - Moisten the swab in sterile normal saline, insert through rectal sphincter, rotate and withdraw
 - Inoculate the specimen in a transport medium such as Cary and Blair transport medium

- Fresh stools
 - Collect during the early stage of the disease and before antimicrobial therapy has been initiated
 - Collect in a clean, preferably sterile, screw-capped container w/o disinfectant or detergent residue
 - Collect from freshly voided stool containing blood and mucus
 - Process the collected stool specimen within two hours, preferably 1 hour
 - Refrigeration is essential if cannot be examined within 2 hrs
 - Not contaminated with urine or water
 - Interfering substances: antibiotics, laxatives, antacids, cathartics, antidiarrheal agents, enemas