Cyclosporiasis: Detecting, Investigating, and Preventing Cases and Outbreaks of this Foodborne Parasitic Disease

Clinician Outreach and Communication Activity (COCA) Webinar
June 18, 2015
Accrediting Statements

CME: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME®) to provide continuing medical education for physicians. The Centers for Disease Control and Prevention designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CNE: The Centers for Disease Control and Prevention is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center’s Commission on Accreditation. This activity provides 1.0 contact hours.

IACET CEU: The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. The CDC is authorized by IACET to offer 0.1 ANSI/IACET CEU’s for this program.

CECH: Sponsored by the Centers for Disease Control and Prevention, a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is designated for Certified Health Education Specialists (CHES) and/or Master Certified Health Education Specialists (MCHES) to receive up to 1.0 total Category I continuing education contact hours. Maximum advanced level continuing education contact hours available are 0. CDC provider number GA0082.

CPE: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is a designated event for pharmacists to receive 0.1 CEUs in pharmacy education. The Universal Activity Number is 0387-0000-15-099-L04-P and enduring 0387-0000-15-099-H04-P. This program is knowledge based.

AAVSB/RACE: This program was reviewed and approved by the AAVSB RACE program for 1.2 hours of continuing education in jurisdictions which recognize AAVSB RACE approval. Please contact the AAVSB RACE program if you have any comments/concerns regarding this program’s validity or relevancy to the veterinary profession.
Continuing Education Disclaimer

CDC, our planners, presenters, and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Planners have reviewed content to ensure there is no bias. This presentation will not include any discussion of the unlabeled use of a product or products under investigational use, with the exception of discussion on the unlabeled use of the antimicrobial combination trimethoprim-sulfamethoxazole to treat cyclosporiasis.
Objectives

At the conclusion of this session, the participant will be able to:

- Discuss what is known about how and where *Cyclospora cayetanensis* is transmitted
- Describe the available approaches for diagnosing, treating, and preventing *Cyclospora* infection, including the limitations of the approaches
- Explain why timely reporting of *Cyclospora* cases to public health authorities is essential
- Discuss the reported U.S. foodborne outbreaks of cyclosporiasis, including the findings and constraints of the outbreak investigations
TODAY’S PRESENTER

Barbara L. Herwaldt, MD, MPH
CAPT, US Public Health Service
Medical Epidemiologist
Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention
Cyclosporiasis is an enteric illness caused by *Cyclospora cayetanensis*, an enigmatic emerging parasite, which was named as recently as the early 1990s & has repeatedly caused U.S. foodborne outbreaks.
Cyclospora’s timeline*

Outbreaks

'77 1st 3 documented cases of infection with “undescribed coccidian” diagnosed in Papua New Guinea
'79
'80
'81
'82
'83 1st documented cases in Haiti (“Big Crypto”), in patients with AIDS
'84
'85 1st documented case in Peru (“Cryptosporidium muris-like object”)
'86 1st documented U.S. cases, in 4 travelers returning from Haiti and Mexico
'87
'88
'89 1st documented cases in Nepal, in 55 foreigners
'90
'91 Name “cyanobacterium-like or coccidian-like body (CLB)” used
'92
'93 Organism confirmed to be a coccidian parasite
'94 Name *Cyclospora cayetanensis* proposed
'95 Trimethoprim-sulfamethoxazole shown to be effective
'96 Phylogenetic relationship to *Eimeria* species shown
'97
'98
'99

Other occurrences

Waterborne outbreak (Pokhara, Nepal)

What type of microbe?

Many

Multiple foodborne outbreaks in North America linked to various types of fresh produce

→... 2015 (It’s not “going away”)

(* Herwaldt BL. Clin Infect Dis 2000;31:1040–57.*)
### Cyclospora cayetanensis: Knowns & unknowns

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Now known</th>
<th>Still unknown</th>
</tr>
</thead>
</table>
| **Parasite** (not an alga or fungus) | - Protozoan (ie, unicellular)  
- Coccidian (oocysts not cysts) | Do other *Cyclospora* species infect humans? |

<table>
<thead>
<tr>
<th>Host</th>
<th>Now known</th>
<th>Still unknown</th>
</tr>
</thead>
</table>
| **Humans** | - Gastrointestinal tract  
- Asexual & sexual stages | Are there any nonhuman hosts of *C. cayetanensis*? |

<table>
<thead>
<tr>
<th>Extrinsic maturation</th>
<th>Now known</th>
<th>Still unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not infective when shed in stool</strong></td>
<td>- Requires days to weeks to sporulate &amp; become infective</td>
<td>How quickly can the parasite sporulate under optimal environmental conditions?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transmission</th>
<th>Now known</th>
<th>Still unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fecally contaminated food / H₂O</strong></td>
<td>- No risk if ingest unsporulated oocysts, even if large inoculum</td>
<td>What accounts for seasonality of cases, which varies among <em>Cyclospora</em>-endemic regions?</td>
</tr>
</tbody>
</table>
Graphic illustration

Microscopy (DIC)

2 sporocysts

4 sporozoites

unsporulated

sporulated

Microscopy (DIC)

(undifferentiated cytoplasm)

(fully differentiated)

sporulation

(Herwaldt BL. In Institute of Medicine, ed. National Academies Press; 2006:85–115, 133–40.)
Relative sizes of microbes

Giardia

Cyclospora

Cryptosporidium

Bacteria

Virus

(8 - 10 micrometers)

(Herwaldt BL. Clin Infect Dis 2000;31:1040–57.)
**Cyclospora: Transmission & risk factors**

- Infected people shed an immature form of the parasite in their feces, which has to mature (*sporulate*) to become infective
  - Environmental conditions conducive to oocyst sporulation & survival are poorly understood
  - Direct person-to-person transmission is highly unlikely

- **Two well-established risk factors for U.S. cases:**
  - International travel to cyclosporiasis-endemic regions (eg, in parts of the tropics & subtropics)
  - Domestic consumption of contaminated fresh produce imported from such regions
Prevention of *Cyclospora* infection

- Persons planning to travel to the tropics or subtropics should be told that **food & water precautions** for *Cyclospora* are similar to those for other intestinal pathogens—**except** that:
  - *Cyclospora* is **not** likely to be killed by routine chemical disinfection or sanitizing methods (eg, with chlorine or iodine)

- **No *Cyclospora* vaccine is available**
Clinical features of symptomatic *Cyclospora* infection

- The incubation period typically is ~1 week (range, ~2 days to 2+ weeks)—which adds to delays in detecting & investigating cases & outbreaks

- The most common symptom is watery diarrhea, which can be profuse
  - Other common abdominal symptoms include anorexia, weight loss, bloating/gas, cramps/pain, & nausea
  - Body aches & low-grade fever may be noted

- *If untreated*, the illness may last for days to weeks to months, with remitting-relapsing symptoms—ie, *not* a brief, trivial illness
  - Substantial weight loss & prolonged fatigue commonly occur
## Symptoms of *Cyclospora* infection

(1996 US outbreak*; N = 760 case-patients with available data†)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea <em>(watery; not bloody)</em></td>
<td>99%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>93%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>92%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>91%</td>
</tr>
<tr>
<td>Bloating / gas</td>
<td>84%</td>
</tr>
<tr>
<td>Abdominal cramps / pain</td>
<td>75%</td>
</tr>
<tr>
<td>Nausea</td>
<td>71%</td>
</tr>
<tr>
<td>Aches</td>
<td>66%</td>
</tr>
<tr>
<td>Fever <em>(typically, low grade)</em></td>
<td>54%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27%</td>
</tr>
</tbody>
</table>


† The number with available data differed for the various symptoms.
Diagnosis of *Cyclospora* infection

*If indicated, consider the diagnosis & request testing:*

- Stool specimens examined for ova & parasites (O & P) usually are *not* examined for *Cyclospora* unless such testing is requested *explicitly*.

- *Even persons with profuse diarrhea might not* shed enough *Cyclospora* oocysts to be readily detectable:
  - Several specimens, from different days, may need to be examined
  - The lab should use sensitive recovery & detection methods

- CDC & other reference labs can provide diagnostic assistance & confirmatory testing, using microscopic & molecular techniques

**Not available:** methods to culture (or propagate / maintain) the parasite, molecular tools for strain differentiation, serologic assays, ....
Cyclospora oocysts are autofluorescent
(UV fluorescence microscopy)
Detection of *Cyclospora* oocysts by microscopy

**Easy to miss**
(blends in with background on an unstained slide)

**Easy to spot**
(autofluorescent)

**Variously acid fast**
(not all oocysts retain the stain)
Treatment of *Cyclospora* infection

- The treatment of choice is trimethoprim-sulfamethoxazole (TMP/SMX)*
  - Typical regimen for immunocompetent adults is 1 double-strength tablet (*TMP 160 mg; SMX 800 mg*), twice a day, for 7 to 10 days

- **No highly effective** alternatives to TMP/SMX have been identified yet for persons who are allergic to or cannot tolerate TMP/SMX

- The fact that the therapy (ie, TMP/SMX) **differs** from the medications used for most other enteric protozoan infections (eg, giardiasis, amebiasis, cryptosporidiosis) highlights the importance of diagnosing infection rather than treating empirically

* Off-label use (not an FDA-approved indication)
Cyclospora’s timeline: what was known & what occurred in & since the mid-1990s*

- 1977: 1st 3 documented cases of infection with “undescribed coccidian” diagnosed in
- 1978: Papua New Guinea
- 1979
- 1980
- 1981
- 1982
- 1983: 1st documented cases in Haiti ("Big Crypto"), in patients with AIDS
- 1984
- 1985: 1st documented case in Peru ("Cryptosporidium muris-like object")
- 1986: 1st documented U.S. cases, in 4 travelers returning from Haiti and Mexico
- 1987
- 1988
- 1989: 1st documented cases in Nepal, in 55 foreigners
- 1990
- 1991: Name “cyanobacterium-like or coccidian-like body (CLB)” used
- 1992
- 1993: Organism confirmed to be a coccidian parasite
- 1994: Name Cyclospora cayetanensis proposed
- 1995: Trimethoprim-sulfamethoxazole shown to be effective
- 1996: Phylogenetic relationship to Eimeria species shown
- 1997
- 1998
- 1999

=> ... 2015 (It’s not “going away”)

Who would have predicted that a protozoan parasite would repeatedly cause large foodborne outbreaks?
The series of spring outbreaks of cyclosporiasis linked to Guatemalan raspberries underscores recurring themes & challenges

1,465 reported cases
(20 states, Wash DC, 2 provinces)

1,012 reported cases
(17 states, Wash DC, 2 provinces)

(harbingers)
(70 reported cases; 2 eastern states)
Cyclospora oocysts, cases, & outbreaks are easily missed
— 1 oocyst, 1 tech, 1 case, 1 call ... can make a difference —

In the large, multistate outbreaks in 1996 & 1997 ....

- **1996:** Index cases were detected in 2 states that had lab personnel with unusual expertise regarding *Cyclospora*

- **1997:** Several index cases/clusters were detected because of unusual circumstances (eg, case-patients were health professionals who knew to consider the diagnosis of *Cyclospora* infection)
Fresh produce often is served in mixtures & inconspicuous ways (eg, garnishes)

— Look for commonalities among different case clusters & for epidemiologic associations with illness —

Would you even remember this garnish? Would the chef? Would the details be specified on the menu or other records?
Raspberries were the common theme
Traceback investigations for fresh produce often are very challenging.

Meal(s) or event(s) → Restaurant(s), caterer(s), retailer(s) → Local distributor(s) → Importer(s) → Exporter(s) → Farm(s)

Compelling, aggregate, multi-cluster traceback data linked the implicated raspberries to Guatemala.
Guatemalan raspberries: suspension of exports

- On May 30, 1997—at FDA’s request—the government of Guatemala & the Guatemalan Berry Commission announced their decision to voluntarily suspend exports of fresh raspberries to the United States.

- Shipments could resume in mid-August 1997.

- In 1998, as planned, shipments were suspended from mid-March through mid-August.
  - But this applied only to the United States—not to Canada.
Spring 1998: evidence from an inadvertent intervention trial
— Canada (not USA) imported Guatemalan raspberries & had an outbreak —

- 1,465 cases (US & Canada)
- 1,012 cases (US & Canada)
- 315 reported cases (Canada)

(70 cases; 2 eastern states)

Canadian (not U.S.) outbreak linked to Guatemalan raspberries
It is very unusual to have implicated produce items still available for *Cyclospora* testing
Spring 2000: Evidence regarding Guatemalan raspberries was strengthened further by detection of *Cyclospora* DNA in frozen leftovers of an epidemiologically implicated food item.

- **1,465 cases** (US & Canada) in 1995
- **1,012 cases** (US & Canada) in 1996 (harbingers)
- **315 cases** (Canada) in 1997
- **1995**
- **1996**
- **1997**
- **1998**
- **1999**
- **2000**

Wedding cake—which had raspberry pieces in a cream filling—tested positive in *Cyclospora* PCR analyses at CDC & FDA (Ho AY, et al. Emerg Infect Dis 2002.)
Route(s) of contamination of the raspberries unknown
— Unproven hypothesis: via contaminated water —

Pesticides, fungicides, insecticides, etc, were mixed in water & sprayed on the raspberries

Drip irrigation
(on ground; not near berries)

Spraying berries
Not just raspberries
Not just Guatemala
Not just spring
Not just 1 vehicle per year
Not just 1 source per vehicle
1997: a series of 5 outbreaks of cyclosporiasis
— by month(s) of exposure (eg, social events)

- March & April: Florida
  - Mesclun lettuce from Peru (see Dec 1997; aggregate evidence)

- April & May: USA & Canada
  - Raspberries from Guatemala

- June & July: Washington DC / Baltimore metro area
  - Basil (multiple possible sources)

- September: Virginia
  - Fruit plate (which ingredient?—only 1 cluster of cases was identified; no opportunities to triangulate)

- December: Florida
  - Salad (mesclun lettuce; aggregate evidence)
The series of U.S. foodborne outbreaks of cyclosporiasis

- **Large outbreaks in the mid-1990s**
  - 1996: multistate outbreak linked to fresh raspberries from Guatemala
  - 1997: multistate outbreak linked to Guatemalan raspberries; also, outbreaks linked to mesclun lettuce (Peru) & basil (>1 possible source)

- **Outbreaks detected almost every year thereafter**
  - Food vehicles/sources not always identified; but examples include raspberries & snow peas (Guatemala), basil (Peru), & cilantro (Mexico)
  - To date, no commercially frozen produce implicated

- **Route(s) of produce contamination not definitively established**

- **Some outbreak investigations led to interventions & prevention measures**
... 2013–2014 ...
2013: U.S. outbreaks of cyclosporiasis

• In late June 2013, public health officials in Iowa & Nebraska began receiving reports of lab-confirmed *Cyclospora* cases not associated with international travel (during 2-week period before symptom onset)

• Overall, a total of 631 such cases, with onset dates during June–August, were reported by 25 states
  - 497 cases (79%) were from 3 states: Texas, Iowa, & Nebraska
2013: Laboratory-confirmed U.S. cases of cyclosporiasis (N = 631*), by state

* Lab-confirmed infection in a person with illness onset during June–August, without known travel outside USA/Canada in 14-day period before onset.

† Includes 1 case that may have been acquired out of state. ‡ Includes 2 cases that may have been acquired out of state. ¶ Might include an international travel-associated case.
2013: Laboratory-confirmed U.S. cases of cyclosporiasis — by groups of states & week of illness onset (N = 631*)

* Lab-confirmed infection in a person with illness onset during June–August, without known travel outside USA/Canada in 14-day period before onset
In 2013, at least 2 distinct outbreaks occurred—linked by epi & traceback data to different types of fresh produce from different parts of Mexico (MX)

• **Iowa & Nebraska**: Restaurant-associated cases were linked to a bagged salad mix (iceberg/romaine lettuces, carrots, red cabbage) from Taylor Farms in Guanajuato, MX
  - What was pertinent ingredient(s) in the mix?

• **Texas**: Some case clusters were associated with *cilantro* from Puebla, MX
  - In 2014, another *Cyclospora* outbreak in Texas was linked to *cilantro* from Puebla, which strengthened the evidence

The bulk of the reported domestically acquired *Cyclospora* cases in 2013 & 2014 were **not directly** linked to food vehicle(s)
C. cayetanensis: Advanced Molecular Detection

• No molecular tools are available yet that can distinguish among strains of the parasite

• Development of such tools is a high priority

• Availability of such tools in the future could help public health investigators determine if cases are linked to each other & to particular food items & sources
Cyclosporiasis is a nationally notifiable disease

*Prompt* reporting & investigations of cases & outbreaks are essential

The fastest surveillance system ....
Consider the diagnosis of *Cyclospora* infection for persons with persistent or remitting-relapsing diarrheal illness

- regardless of whether they have a history of international travel
- regardless of the time of year—*but especially* during spring & summer

*If indicated, explicitly* request laboratory testing for this parasite per se

*Promptly* report confirmed & suspected cases to public health authorities

- *Even* seemingly isolated cases could be part of outbreaks
Whither *Cyclospora*?

... 2015 ...?
Continuing Education guidelines require that the attendance of all who participate in COCA Conference Calls be properly documented. All Continuing Education credits/contact hours (CME, CNE, CEU, CECH, ACPE and AAVSB/RACE) for COCA Conference Calls/Webinars are issued online through the [CDC Training & Continuing Education Online system](http://www.cdc.gov/TCEOnline/).

Those who participate in the COCA Conference Calls and who wish to receive CE credit/contact hours and will complete the online evaluation by **July 17, 2015** will use the course code **WC2286**. Those who wish to receive CE credits/contact hours and will complete the online evaluation between **July 18, 2015** and **June 17, 2016** will use course code **WD2286**. CE certificates can be printed immediately upon completion of your online evaluation. A cumulative transcript of all CDC/ATSDR CE’s obtained through the CDC Training & Continuing Education Online System will be maintained for each user.
Thank you for joining!
Please email us questions at coca@cdc.gov

Centers for Disease Control and Prevention
Atlanta, Georgia
http://emergency.cdc.gov/coca
Join Us on Facebook

CDC Facebook page for Health Partners! “Like” our page today to receive COCA updates, guidance, and situational awareness about preparing for and responding to public health emergencies

CDC Health Partners Outreach
http://www.facebook.com/CDCHealthPartnersOutreach