Anaerobic infections

PART 2: Infection with Gram-positive obligate anaerobes (toxigenic Clostridium spp.)

Prof. Cary Engleberg, M.D.
Division of Infectious Diseases,
Department of Internal Medicine

Unless otherwise noted, this material is made available under the terms of the **Creative Commons Attribution 3.0 License**: http://creativecommons.org/licenses/by/3.0/

Disclaimers

- I have reviewed this material in accordance with U.S. Copyright Law and have tried to maximize your ability to use, share, and adapt it. The citation key on the following slide provides information about how you may share and adapt this material.
- Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarification regarding the use of content.
- For more information about how to cite these materials visit http://open.umich.edu/education/about/terms-of-use.
- Any medical information in this material is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. Please speak to your physician if you have questions about your medical condition.
- Viewer discretion is advised: Some medical content is graphic and may not be suitable for all viewers.

Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- PD-GOV **Public Domain – Government**: Works that are produced by the U.S. Government. (17 USC § 105)
- PD-EXP **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.
- PD-SELF **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.
- ZERO **Creative Commons – Zero Waiver**
- BY **Creative Commons – Attribution License**
- BY-SA **Creative Commons – Attribution Share Alike License**
- BY-NC **Creative Commons – Attribution Noncommercial License**
- BY-NC-SA **Creative Commons – Attribution Noncommercial Share Alike License**
- GNU-FDL **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- PD-INEL **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

- © FAIR USE **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

  Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

  To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

Sources of Anaerobic Infections

- Usually endogenous
  - Intestinal anaerobes
  - Oral anaerobes
- Usually exogenous
  - *Clostridium tetani* (tetanus)
  - *Clostridium botulinum* (botulism)
  - *Clostridium difficile* (antibiotic-associated colitis)
- Either endogenous or exogenous
  - Other Clostridial infections (e.g., gas gangrene)

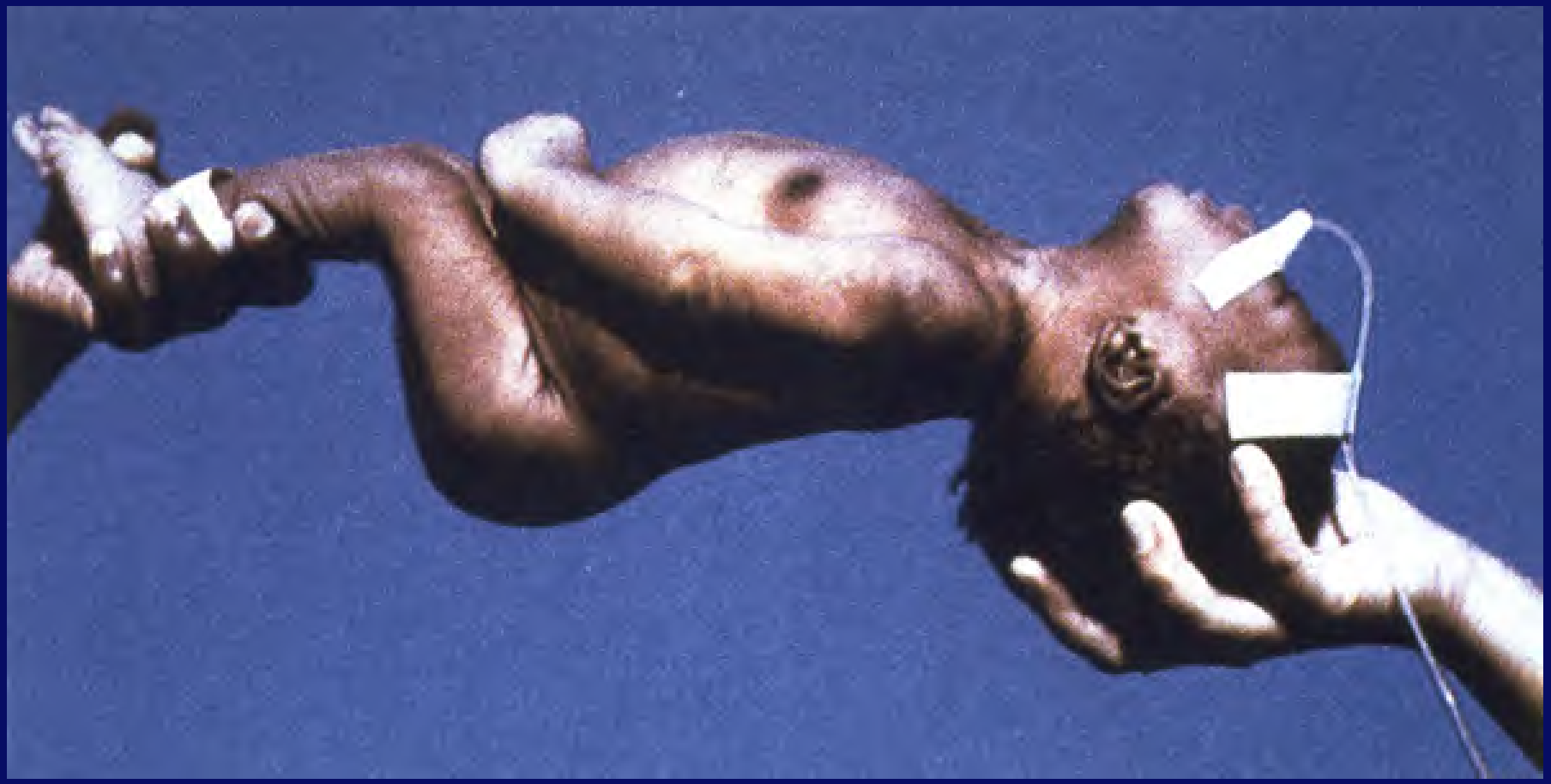
What are these lectures about?

- *Part 1: Invasive Clostridium spp.*
  - gas gangrene/myonecrosis — *C. perfringens, C. septicum, C. histolyticum, C. novyi,* etc.
  - wound infection/abscess
  - food poisoning — *C. perfringens*
- *Part 2: Toxigenic Clostridium spp.*
  - tetanus — *C. tetani*
  - botulism — *C. botulinum*
  - antibiotic-associated colitis — *C. difficile*
- *Part 3: Gram-negative anaerobes*
  - abscesses — *B. fragilis, Bacteroides spp, Prevotella, Porphyromonas, Fusobacterium, anaerobic cocci*
  - other

Case: back spasms in a newborn

- A 10 day old newborn male develops spastic rigidity of the face, neck and back. Minimal movement of the infant's cradle causes repetitive whole body spasms.
- On examination, the infant has a heart rate of 140/min but is afebrile. The umbilical stump appears moist and cyanotic.

Rigidity (tetany)



PD-GOV CDC Public Health Image Library

Clinical features of tetanus

- No fever or sepsis
- Early localized spastic paralysis
- Generalized spastic paralysis
  - Toxin blocks central motor inhibitory impulses
  - Reflex spasms
- Trismus, risus sardonicus, opisthotonos are key signs

Tetanus toxin enters a peripheral nerve and migrates centrally

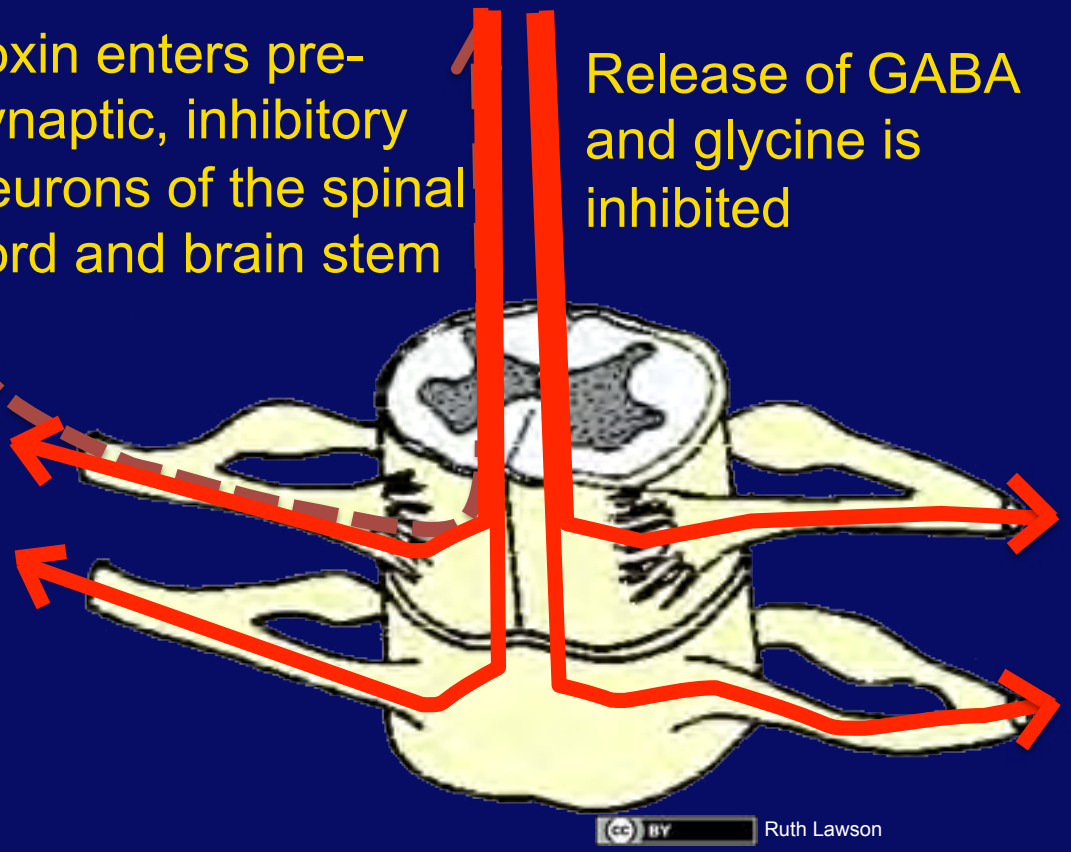
Toxin enters pre-synaptic, inhibitory neurons of the spinal cord and brain stem

Release of GABA and glycine is inhibited

PD-EXP
Agnolo di Cosimo

Organisms grow in the anaerobic wound

C.tetani is inoculated



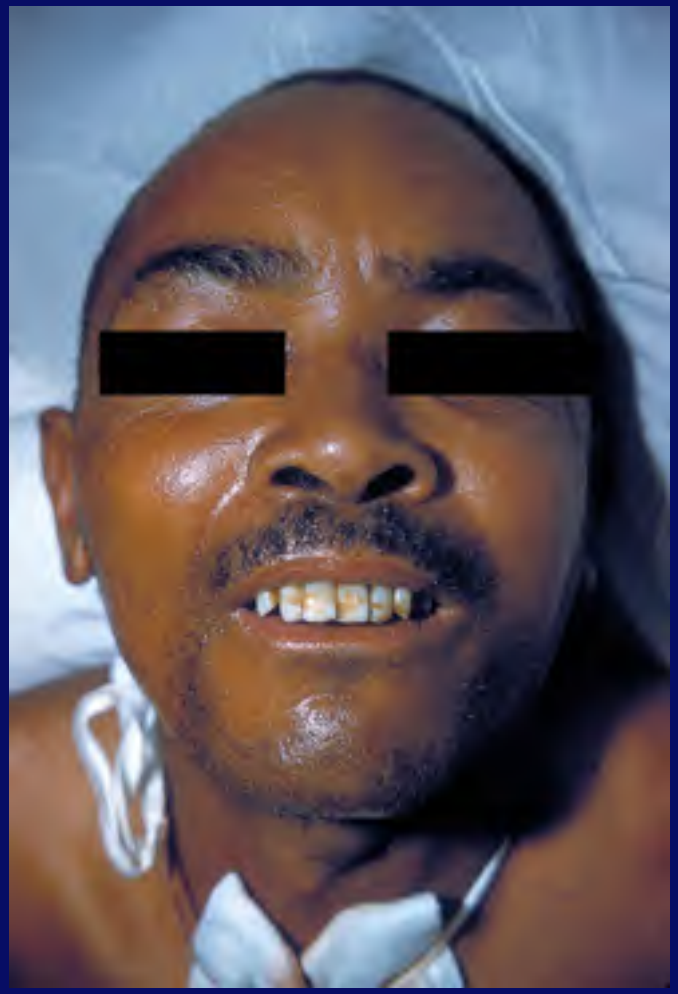
CC BY Ruth Lawson

Stimulatory motor impulses are uninhibited, and tetany occurs

Tetanus toxin mechanism

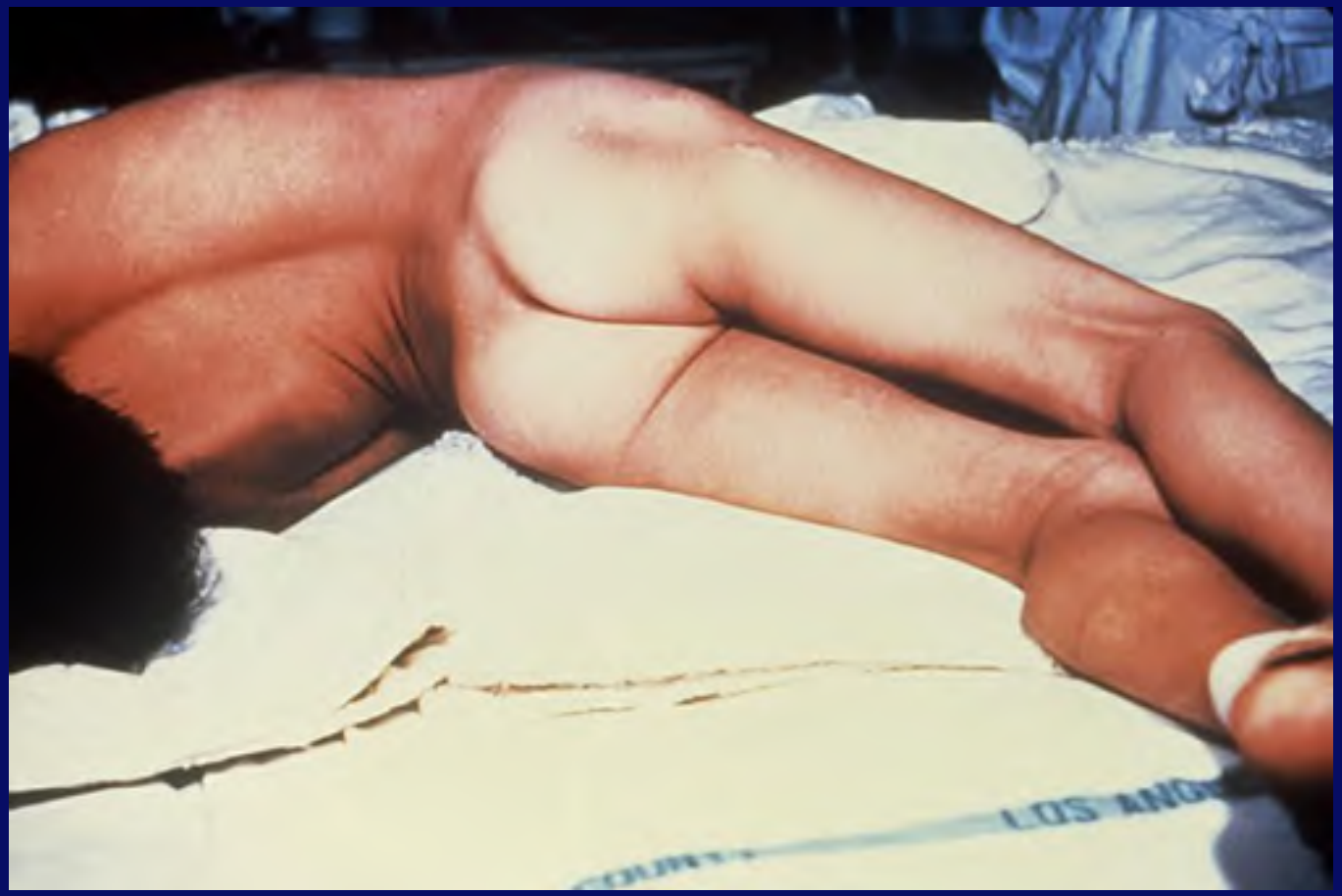
- 150kDa protein exotoxin
  - A-B two-chain toxin, connected by a -S-S- bridge
  - A is a zinc endopeptidase, B is a binding protein
- Toxin enters α-motor neurons at the wound site, is discharged across synapses, and is taken up by pre-synaptic neurons (B subunit binds to specific receptors)
- A subunit is released into cytoplasm
- Degrades synaptobrevin, preventing release of vesicle contents
- Note: There is no significant toxemia

Risus sardonicus



PD-GOV CDC Public Health Image Library

Opisthotonos in an adult



PD-GOV CDC Public Health Image Library

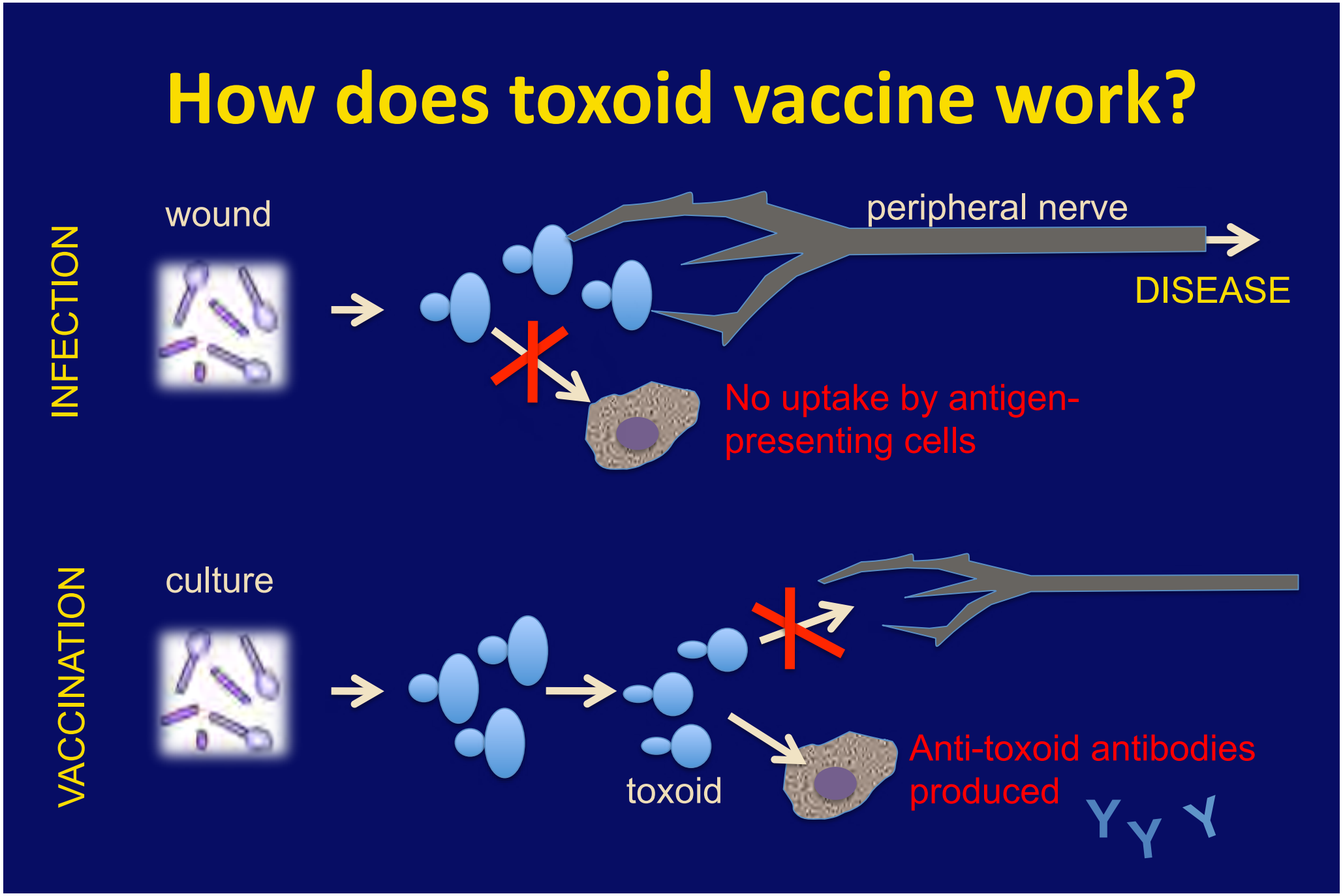
Tetanus-who is at risk?

- Unvaccinated persons with puncture wounds
- Neonates with unsanitary umbilical care
- IV drug users

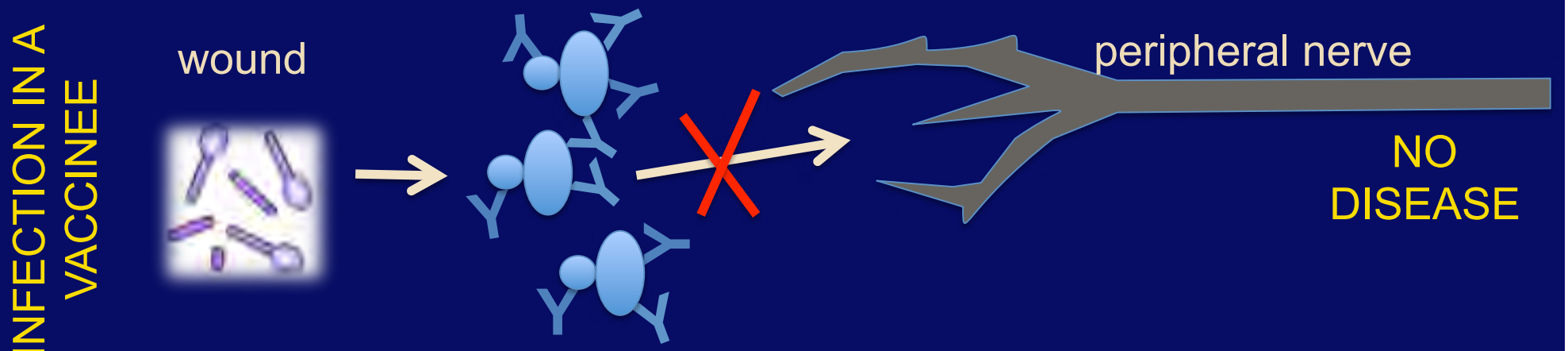
Treatment & Prevention

- Antiserum to toxins to neutralize any free toxin
- Antibiotics (e.g., metronidazole) to kill live organisms
- Physical and respiratory support
- Primary tetanus vaccination (toxoid); priority for unvaccinated pregnant woman
  - N.B. tetanus is a non-immunizing event

How does toxoid vaccine work?



How does toxoid vaccine work?



Anti-toxoid antibodies
bind to and inactivate toxin

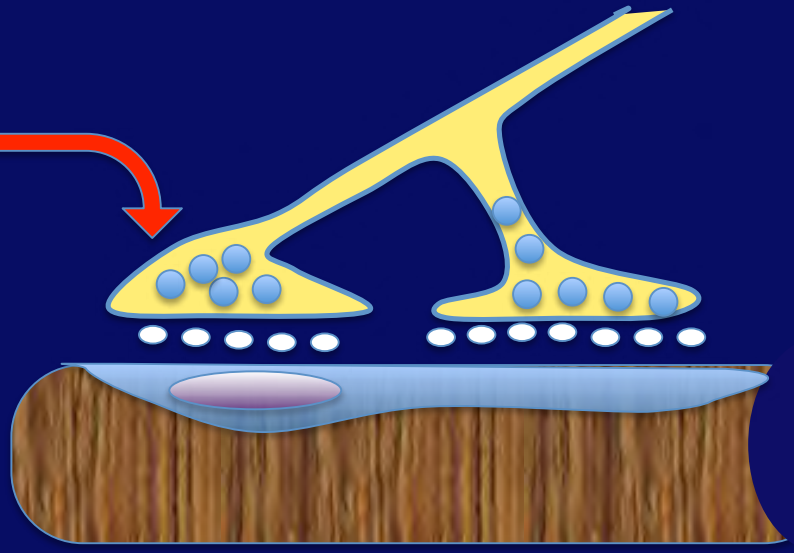
Case: descending paralysis

- 18 hours after eating home-canned string beans, a 38 year old man develops *blurred vision*, *slurred speech*, and *dry mouth*. Within hours, he notes *weakness of the neck and arms* and is having *labored breathing*.
- On physical examination, his vital signs are normal. He is drooling.
- His 34 year old wife also ate some of the beans and is now beginning to have some difficulty swallowing.

Botulism

Improper sterilization;
C. botulinum spores
inoculated

Toxin inhibits acetylcholine release at myoneural junction



Muscle cells

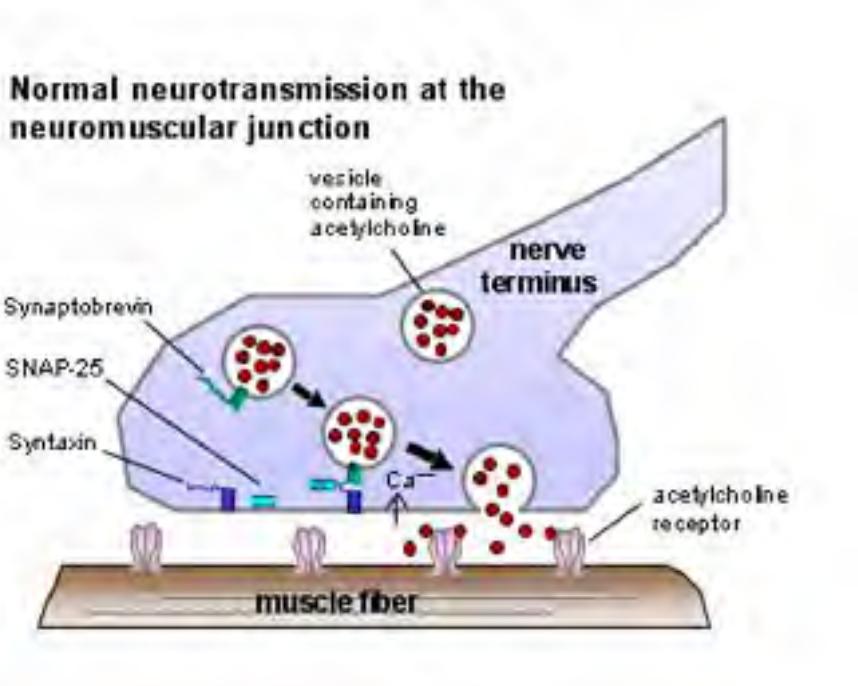
Motor paralysis and respiratory failure

CC BY Theresa Stanton

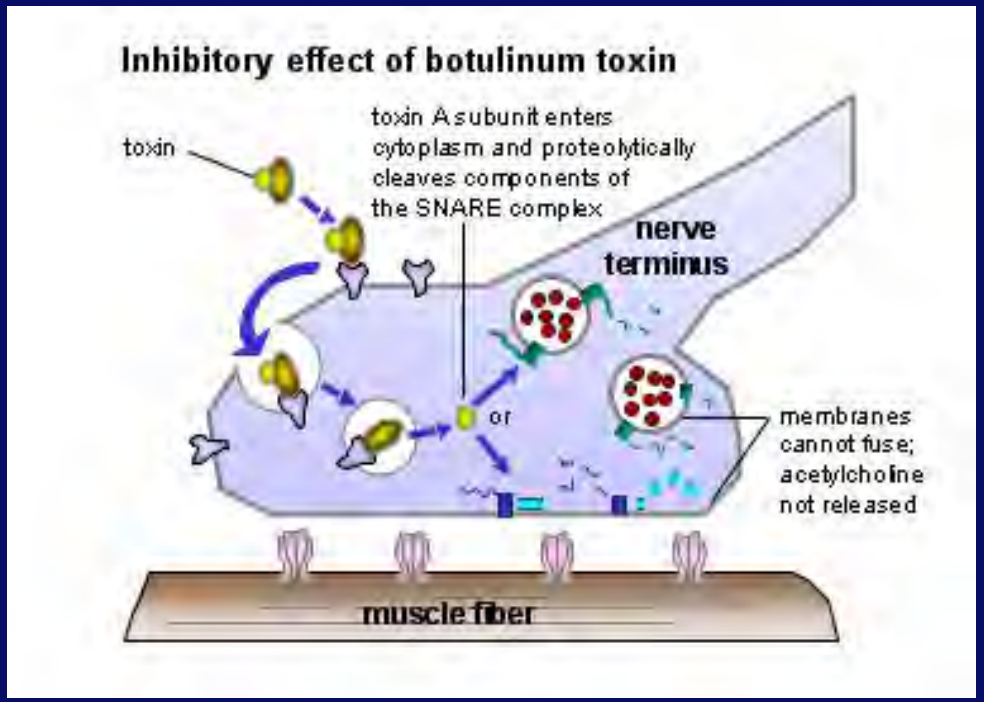
How toxic is it?

- 400mg of pure botulinum toxin is enough to kill everyone on Earth!!

Mechanism of botulinum toxin



PD-INEL Source undetermined



PD-INEL Source undetermined

Other forms of botulism

- Wound botulism
  - (analogous to tetanus)
- Infant botulism
  - flaccidity at 3- 20 weeks
  - ingestion of large numbers of organisms that proliferate and sporulate in the intestine
  - Honey implicated in a large outbreak
  - (+/-analogous to clostridial food poisoning)

Treatment and prevention

- Prompt antitoxin can be life-saving
  - (mortality 100%→25%)
- Airway protection and respiratory support
- There is no vaccine
- Prevention relies on regulated food manufacturing

Case: diarrhea

- An 81-year-old male invalid with dementia has a fever of 38.5°C for 5 days. He was previously well, except for a UTI 4 weeks ago. At that time, he was hospitalized and given ampicillin.
- On P.E., he was comfortable, but confused. Temp = 39°; other vital signs - normal. There were no localized physical findings; abdominal examination-normal.
- A WBC count was 25,000/mm^3

Case (continued)

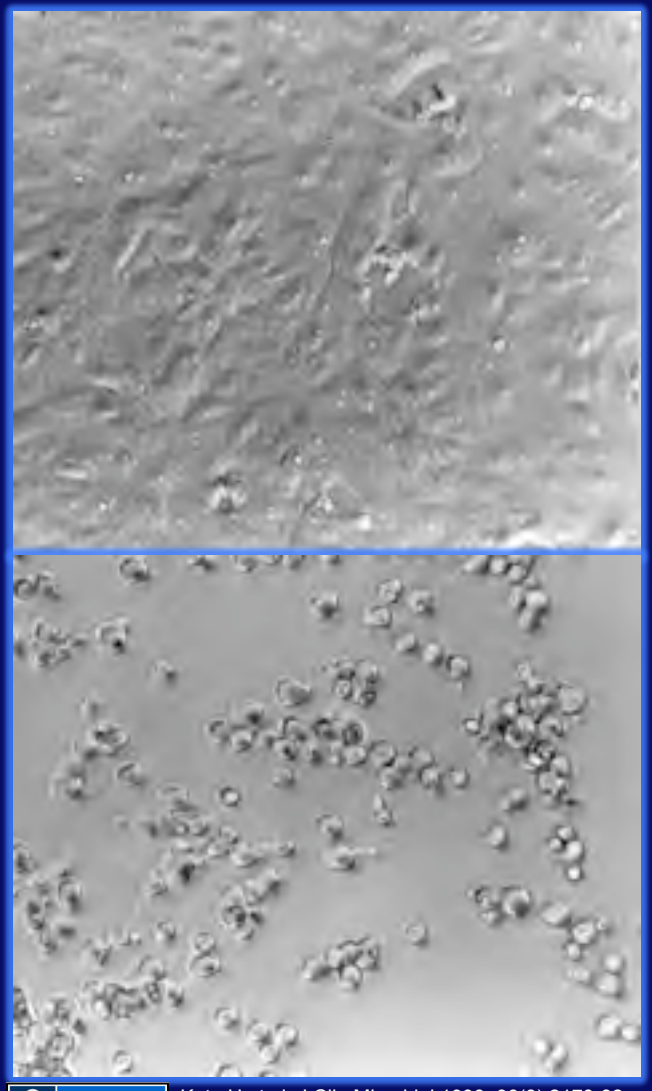
- The next morning, the patient passed two loose bowel movements during the night and another in the morning.
- A stool specimen was positive for occult blood
- Assay of stool for *Clostridium difficile* toxin was positive.
- Treatment was begun with oral metronidazole.
- The patient became afebrile within 36 hours, and he returned to his home without further laboratory investigations within 72 hours.

Questions to consider

- Where do the causative organisms come from?
- Is the history of previous treatment with ampicillin pertinent to *C. difficile* infection?
- What is the role of the spores of *C. difficile* in the disease process?
- What caused the patient's symptoms?
- Could this illness have been fatal?

Background

- Cause of "clindamycin-associated colitis" established in 1978
- Cytotoxin assay on stool filtrate
  - *Most reliable diagnostic test*



Normal Vero cells

Vero cells exposed to stool filtrate

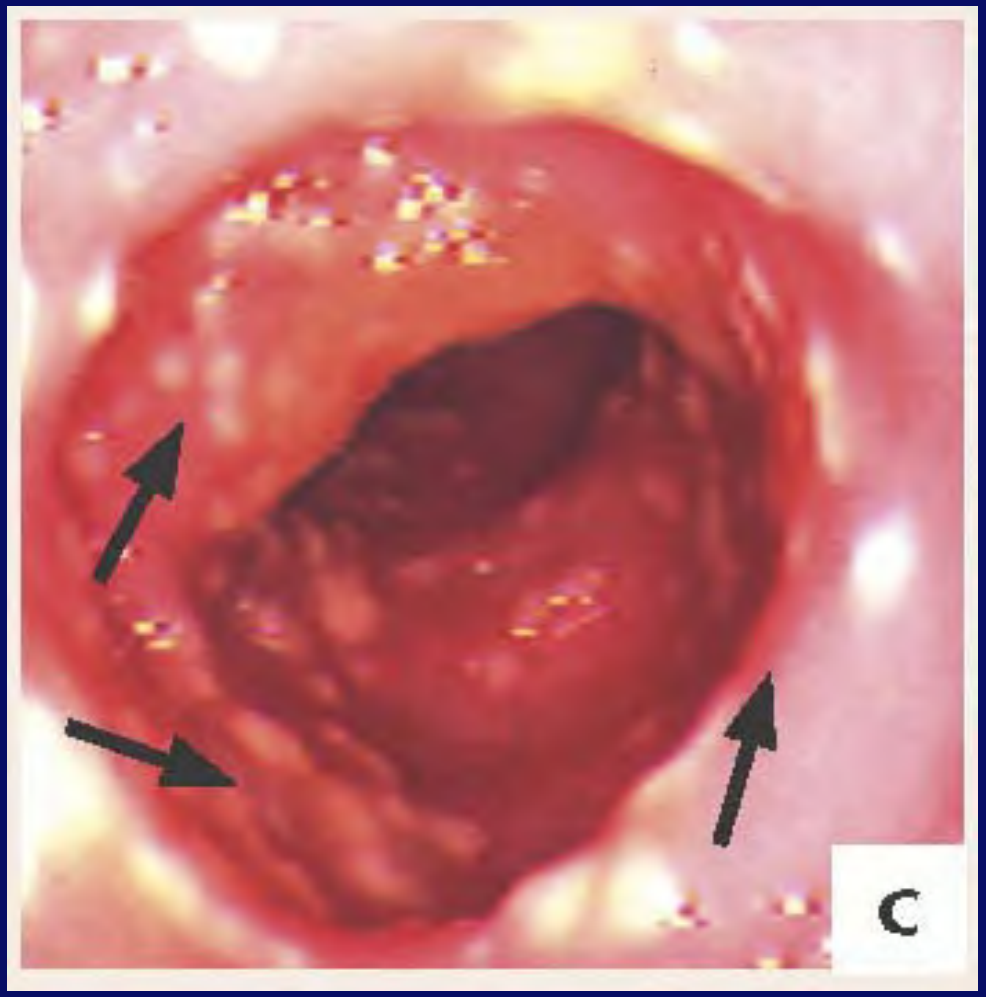
PD-INEL

Kato H et al. J Clin Microbiol 1998; 36(8):2178-82

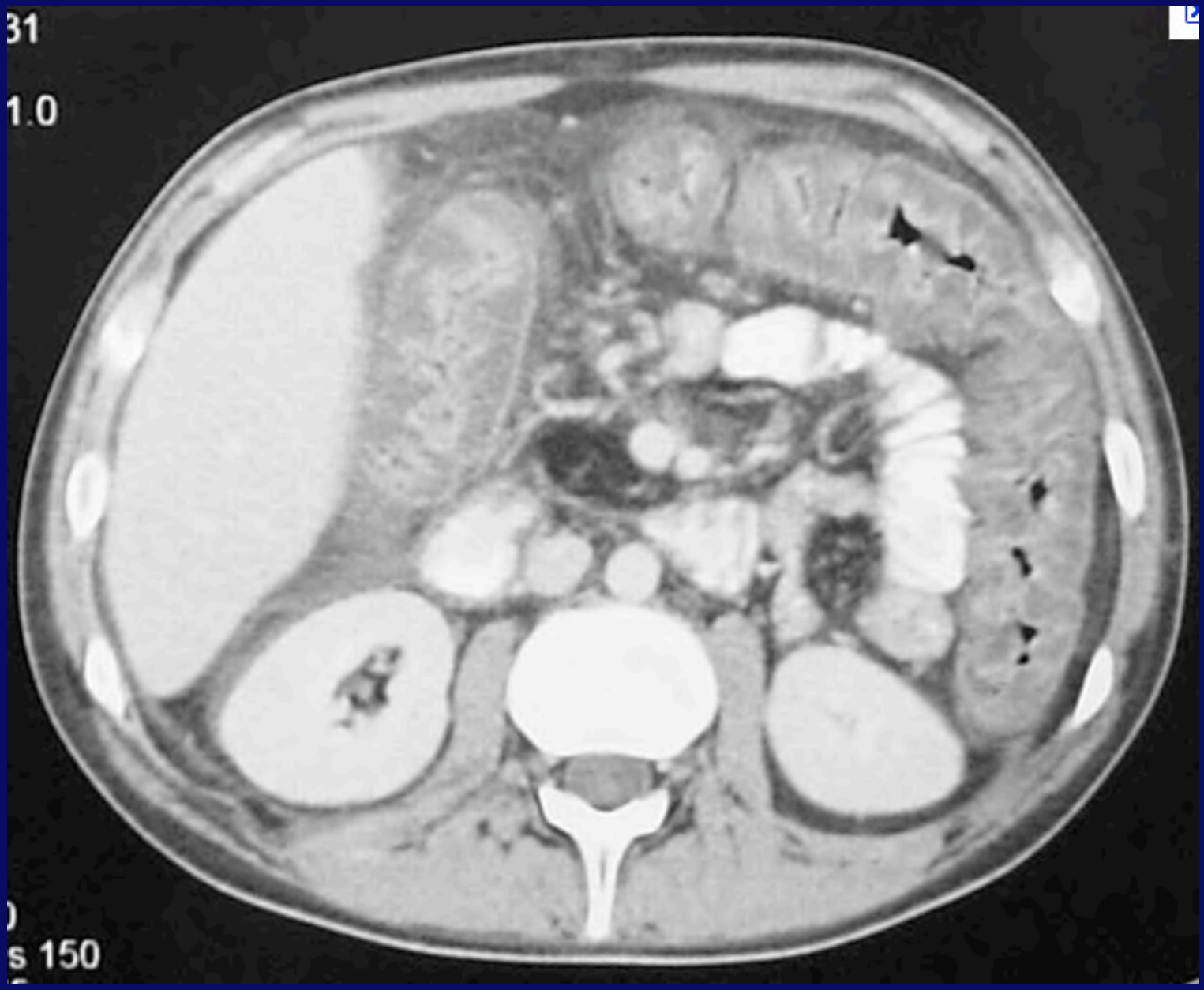
Clinical features of CDI

- Diarrhea, abdominal cramps, fever, fecal WBCs → pseudomembranous colitis (advanced stage)
- Protein-losing enteropathy → hypoalbuminemia and anasarca
- Leukocytosis → leukemoid reaction
- Ileus → megacolon (previously rare)

Endoscopic view of PMC



PD-INEL MW Hull & PL Beck. Canadian Family Phys. 2004; 50:1536-45



PD-INEL Yates et al. Thorax 2007; 62:852-56

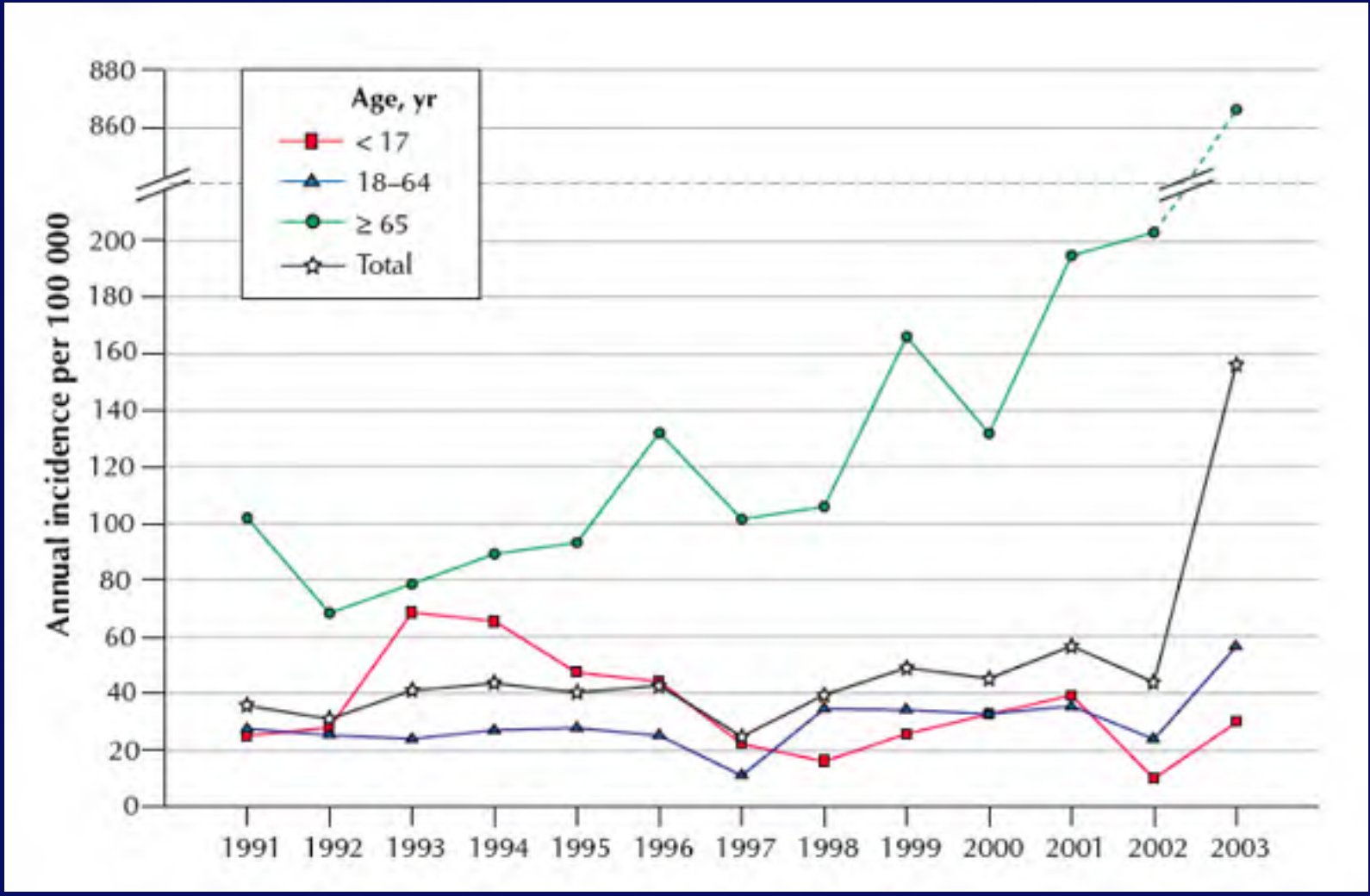
CDI: predisposing factors

- Antibiotic use:
  - *Clindamycin, Ampicillin, Amox (1970s)*
  - *Cephalosporins (1980s)*
  - *Fluoroquinolones (1990s onward)*
- Hospitalization:
  - *Colonization 10x higher in hospitalized adults*
- Advanced age:
  - *Attack rate 20-fold higher in patients >65 vs. <20yrs*
- GI surgery/procedures

C. difficile pathogenesis

- CDI is a disease of the colon (generally it does not affect other parts of the GI tract)
- Establishes itself in the colon only when normal flora is disrupted
- The bacteria are non-invasive
- The disease is caused by bacterial toxins
  - Toxin A = enterotoxin (in most, but not all strains)
  - Toxin B = cytotoxin
- Some asymptomatic patients are culture-positive, but toxin-negative

A Change Noted in Canada



PD-INEL Pepin et al. CMAJ 2004;171(5):466-72

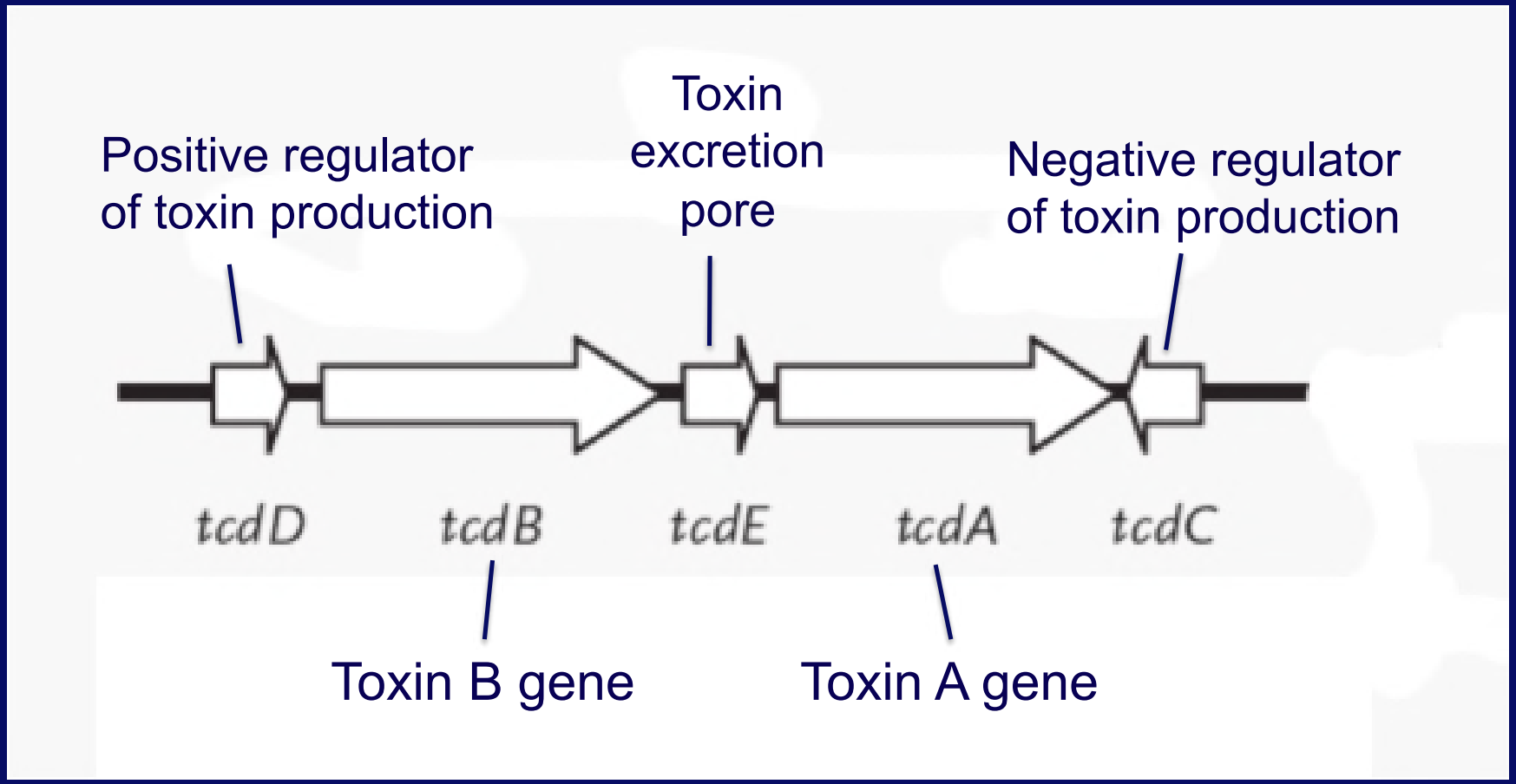
Mortality attributable to CDI, Quebec

Outcome	Group; no. (%) of patients: Case subjects *n* = 161	Control subjects *n* = 656	*p* value
Death			
Within 30 d	37 (23.0)	46 (7.0)	< 0.001
Within 90 d	48 (29.8)	75 (11.4)	< 0.001
Within 6 mo	58 (36.0)	96 (14.6)	< 0.001
Within 1 yr	60 (37.3)	135 (20.6)	< 0.001
Total duration in hospital, mean, d	33.7	23.1	< 0.001
Admission to ICU			
All causes	51 (31.7)	158 (24.1)	0.06
CDAD-related	16 (9.9)	NA	
CDAD-related colectomy	4 (2.5)	NA	

~16%

PD-INEL Pepin et al. CMAJ 2005;173(9)

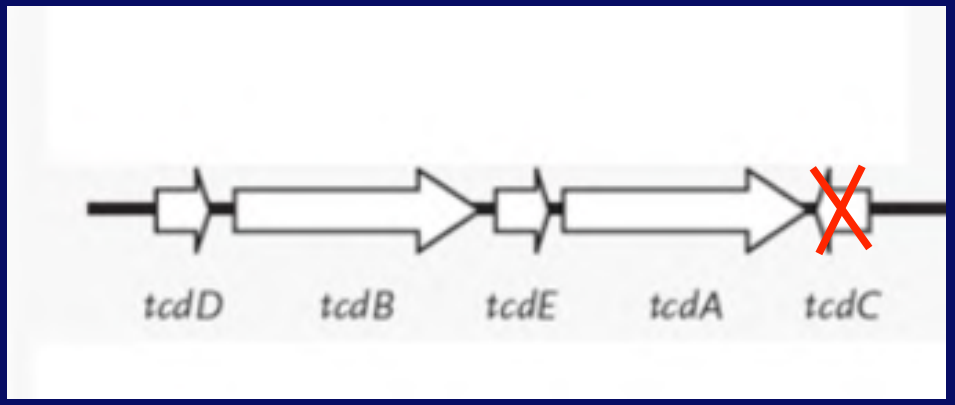
Pathogenicity loci in *C. difficile*



PD-INEL McDonald et al. NEJM 2005; 353:2433-41)

Characteristics of the epidemic strain

- Single clone
- Resistant to fluoroquinolones
- Deletion in *tcdC*
- Encodes a novel binary toxin



PD-INEL McDonald et al. NEJM 2005; 353:2433-41)

BI/NAP1 and severity of disease

Diarrhea Severity	Presence of Δ*tcdC* **and** binary toxin: Yes	Presence of Δ*tcdC* **and** binary toxin: No
Severe	22	0
Non-Severe	110	25

P=0.03

(from Loo et al. NEJM 2005; 353: 2442-9)

Diagnosis of CDI

- Cytotoxin B assay ("gold standard")
- Toxin ELISA test
  - Only ~70-80% sensitive, hence must be repeated to have adequate sensitivity
- Culture alone is *not* useful
- Culture plus cytotoxin assay
- Endoscopy
- Response to metronidazole or vancomycin

Treatment of CDI

- Luminal antibiotics
  - Oral metronidazole,
  - Oral vancomycin (not absorbed)
- ? Probiotics (none proven effective)
- No antimotility agents (contraindicated)

CDI recurrence

- Common among the elderly with severe underlying disease or continued antibiotics
- Persistence of spores in the GI tract
- Treated with long, tapering courses of vancomycin

Where are the spores?

PD-SELF JI Scott

BY-NC-SA Ian Britton

PD-SELF Chris McKenna

BY-SA Jasleen Kaur

BY Royalty-Free/Corbis

Questions to consider

- Where do the causative organisms come from?
- Is the history of previous treatment with ampicillin pertinent to *C. difficile* infection?
- What is the role of the spores of *C. difficile* in the disease process?
- What causes the patient's symptoms?
- Could this illness have been fatal?

Environmental methods to control the spread of CDI

- Hand hygiene: washing with antiseptic soap; not alcohol-based hand gels!
- Environmental surfaces can be cleaned with 1:10 sodium hypochlorite mixed fresh daily
- Isolate and/or cohort patients with CDI in the hospital
- Control 2nd and 3rd generation cephalosporin and fluoroquinolone use
- Treatment of asymptomatic carriers is not helpful

Vaccine?

- There is evidence that luminal antitoxin prevent disease; however,
- There is no effective vaccine currently

Generalizations about clostridia

- Sporulation is important for survival in the environment and for transmission between hosts.
- Disease is mediated by exotoxin-release from vegetative cells
- Simple antibiotics are effective; resistance is not a problem
- Active and passive immunization targets exotoxins

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 7: CDC, Neonatal tetanus, Public Health Image Library, #6374

Slide 8: Agnolo di Cosimo, Cupid's foot, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Monty_python_foot.png (born 1503, died 1572) and Ruth Lawson, Spinal Cord, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Anatomy_and_physiology_of_animals_The_spinal_cord.jpg, CC-BY, http://creativecommons.org/licenses/by/3.0/

Slide 11: CDC, Risus sardonicus, Public Health Image Library, #2857

Slide 12: CDC, Opisthotonus, Public Health Image Library, #6373

Slide 18: Teresa Stanton, Mason Jar, Flickr. Com, http://www.flickr.com/photos/teresa-stanton/503952464/ , CC-BY, http://creativecommons.org/licenses/by/3.0/

Slide 20: Source undetermined, Source undermined

Slide 26: Kato H, Kato N, Watanabe K et al. Identification of toxin A-negative, toxin B-positive *Clostridium difficile* by PCR. J Clin Microbiol. 1998; 36(8):2178-82. Figure 2, http://jcm.asm.org/cgi/content-nw/full/36/8/2178/F2

Slide 28: Hull MW, Beck PL. Clostridium difficile-associated colitis. Canadian Family Physician 2004; 50:1536-45, http://www.cfpc.ca/cfp/2004/nov/vol50-nov-cme-1.asp

Slide 29: Yates B, Murphy DM, Fisher AJ, et al. Pseudomembranous colitis in four patient with cystic fibrosis following lung transplantation. Thorax 2007; 62:552-56, http://thorax.bmj.com/content/62/6/554.full

Slide 32: Pepin J, Valinquette L, Alary M-E, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. Canadian Med Assoc J 2004;171(5):466-72.

Slide 33: Pepin J, Valinquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. Canadian Med Assoc J 2005;173(9) DOI:10.1503/cmaj.050978.

Additional Source Information (cont.)

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 33 & 34: MacDonald LC, Killgore, GE, Thompson A, et al. An Epidemic, Toxin Gene-Variant Strain of *Clostridium difficile*. New Engl J Med 2005; 353(23):2433-41.

Slide 40 (left to right):

- JI Scott, Acute Room, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Acute_Room.JPG
- Chris McKenna, Bathroom Sink, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Bathroom_sink.JPG
- Ian Britton, Computer keyboard, FreeFoto.com (ref no. 04-04-7), http://www.freefoto.com/preview/04-04-7?ffid=04-04-7, CC-BY-NC-ND/3.0, http://creativecommons.org/licenses/by-nc-nd/3.0/
- Jasleen Kaur, Stethoscope, Flickr.com, http://www.flickr.com/photos/jasleen_kaur/4952166117/, CC-BY-SA/2.0, http://creativecommons.org/licenses/by-sa/2.0/
- Royalty Free/Corbis, Doctor, Portrait, Picasa, http://picasaweb.google.com/villages.info, CC-BY, http://creativecommons.org/licenses/by/3.0/