Diagnosis, Management, and Prevention of *Clostridium difficile* infection in Long-Term Care Facilities: A Review

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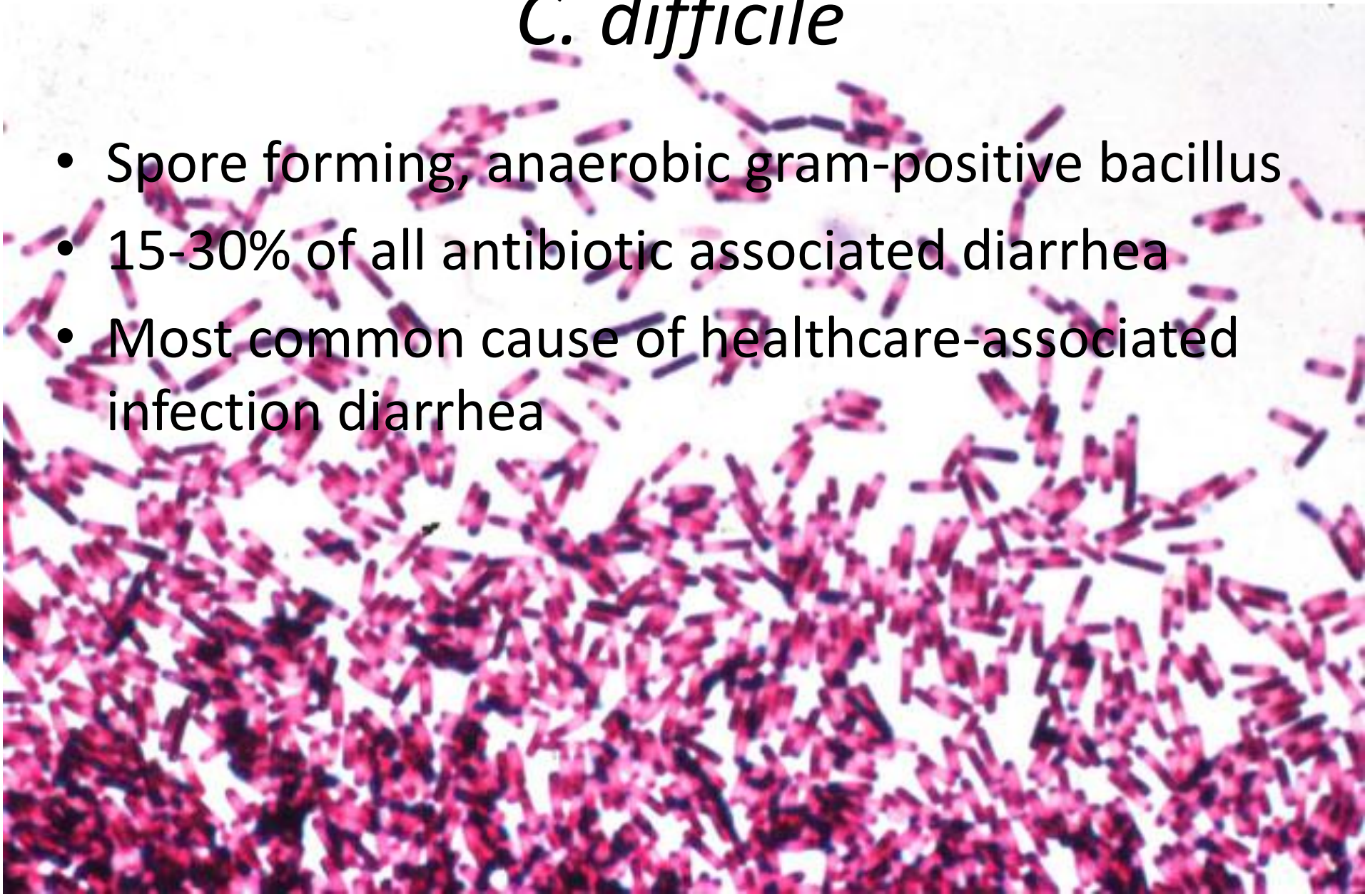
James Kahn and Carolyn Kenney, MSIV

Overview

- Burden of disease associated with *C. difficile*
- Epidemic, hypervirulent *C. difficile*
- Pathogenesis
- Acquisition and transmission in healthcare facilities
- Risk Factors
- Infection in Older Adults and in LCTFs
- Clinical Features and Complications
- Diagnosis
- Treatment
- Prevention and Control in LCTFs

C. difficile



- Spore forming, anaerobic gram-positive bacillus
- 15-30% of all antibiotic associated diarrhea
- Most common cause of healthcare-associated infection diarrhea

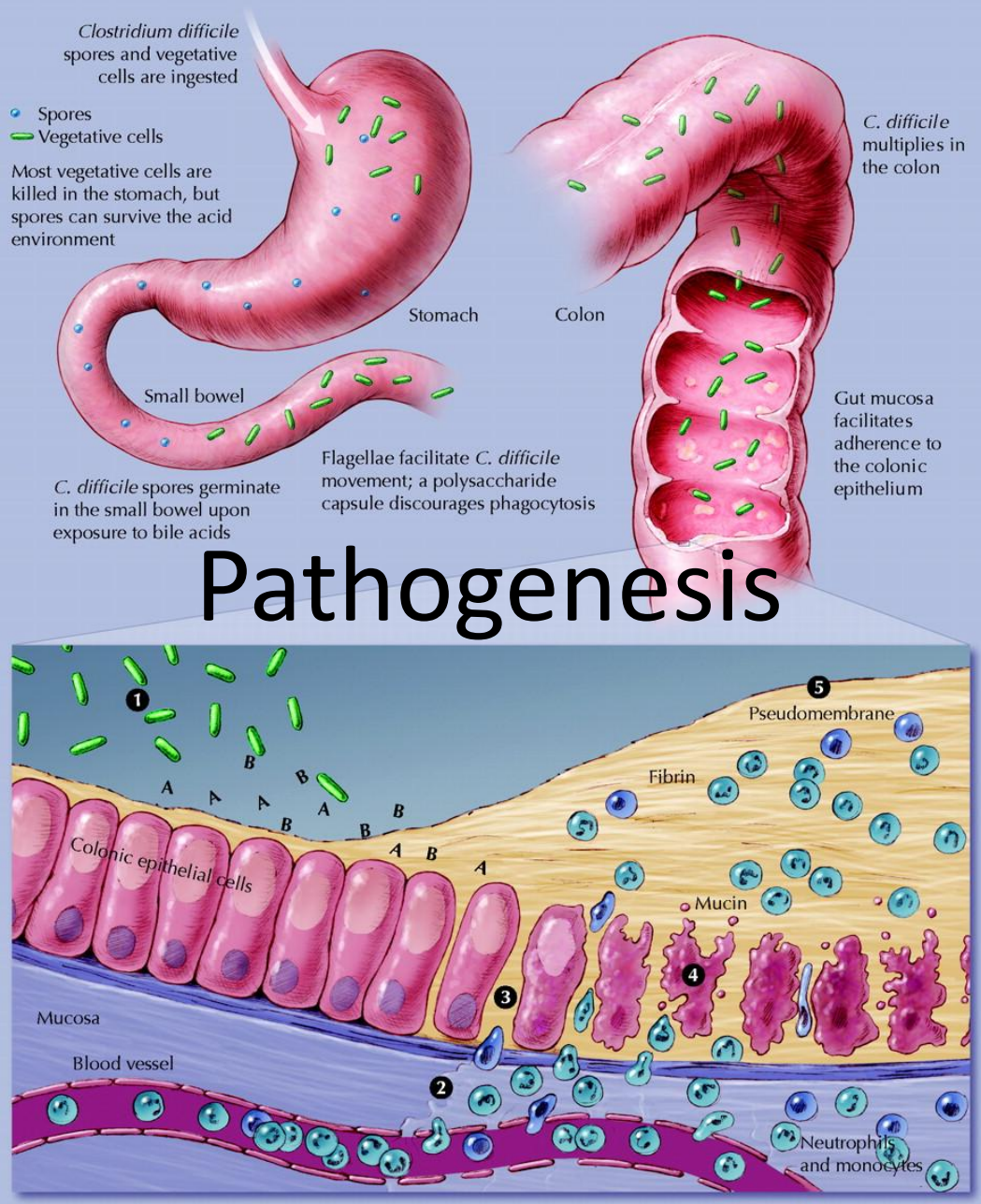
Why do we care?

- Prevalence of 13.2 per 1,000 inpatients
  - 69% were >60 yo
  - 75% thought to have been healthcare associated
- Increases hospital stay by 2.6-4.5 days
- >$1 billion/year spent in U.S. for management of *C. difficile* infection and its complications
- Mortality – 23.7 per million in 2004
  - Geriatric population – 104 per million

Epidemic, Hypervirulent Strain

- Quebec, Canada
  - Increase in incidence in >65 yo -156 per 100,000 population in 1991 to 867 per 100,000 in 2003
  - Excess mortality 6.9% at 30 days and 16.7% at 1 year
- Changes in antimicrobial use, suboptimal infection control, epidemic strains of *C. difficile (*BI/NAP1/027)
  - Hyperproduction of toxins due to 18bp deletion
  - Binary toxin
  - Resistance to fluoroquinolones
  - hypersporulation

Pathogenesis



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (**1**). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (**2**), opening of epithelial cell junctions (**3**) and epithelial cell apoptosis (**4**). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (**5**) and watery diarrhea.

Acquisition and Transmission

- Healthy adults – 2-5% colonized with *C. difficile*
  - Hospitalized patients – 20-40%
- Reservoir
  - Colonized or infected patients
  - Contaminated environment
    - Spores can survive for months – toilet, floor, bedding, furniture, telephones, medical equipment
  - Healthcare worker hand carriage

Table 1. Factors that May Contribute to Greater Risk of *Clostridium difficile* Infection in Older Adults
Frequent receipt of antimicrobial agents
Frequent or prolonged hospitalizations
Presence of underlying comorbid medical conditions
Use of feeding tubes (nasogastric, gastrostomy)
Use of acid suppressant medications
Age-related effects on host defense mechanisms
Decreased gastric acidity
Diminished antibody response to *C. difficile* toxins
Impaired *C. difficile*–specific neutrophil phagocytosis

Severe/complicated infection

- Definition:
  - Infection associated with death
  - Admission to ICU
  - Need for colectomy
- Risk factors: age, admission from another hospital or nursing home
- Associated with complicated disease – leukocytosis (>20K), renal failure (Cr >2.0), hypoalbuminemia (<2.5), SBO or ileus, colorectal inflammation on imaging

Older adults and LTCFs

- Overall increase in *C. difficile* infection rates disproportionately affected older patients
- Prevalence in LTCFs – 14.7%
- Most LTCF residents spontaneously clear in feces within 2-3 months
  - May be asymptomatic in 1/5 for longer period
- LTCF residents at increased risk for severe disease

Clinical features of *C. difficile* infection

- Typical features are watery diarrhea with crampy lower abdominal pain, often accompanied by fever, anorexia and nausea
- Fulminant pseudomembranous colitis – Sx's are usually more severe, with diffuse abdominal pain and distention
- Severe disease often associated with peripheral blood leukocytosis and hypoalbuminemia

Complications of *C. diff* diarrhea

- Dehydration, hypokalemia, GI hemorrhage, toxic megacolon, and colonic perforation in up to 10% of infected individuals
- 15-35% of pts with first episode of infection have recurrence of symptoms within 2 mths regardless of initial antimicrobial treatment
- Risk factors for recurrence are age > 65 yrs, greater severity of underlying disease and reexposure to antimicrobial agents

Diagnosis

- Suspect in any adult with Abx-associated (occurring within 8 weeks of antimicrobial use) or healthcare-associated diarrhea, especially with fever also present
- Abdominal imaging (such as a CT scan) can show ileus with dilated colonic segments or show bowel wall edema or inflammation, evident as “thumbprinting” of colonic mucosa
- The above changes are consistent with (but not specific for) pseudomembranous colitis as this requires direct visualization of colon to determine if present yet this is overall not very sensitive or practical for the diagnosis of *C. diff*
- Therefore diagnosis of *C. diff* infection relies on lab testing to detect the organism or its toxins in diarrheal fecal specimens

Diagnostic Tests

- Most common methods are based on detection of toxins A and B
- Cytotoxin assay – uses tissue culture to detect toxin B and generally has been considered to be the criterion standard for Dx because of its correlation with pseudomembranous colitis
  - Specificity > 97% but sensitivity is 75-85% so false negatives may occur
  - Test requires expertise with tissue culture procedure and takes 48-72 hrs for results

Diagnostic Tests

- Enzyme immunoassays for toxins A and B – rapid (same day), technically simple, relatively inexpensive but have poorer sensitivities (70-85%) and may cause more false-positives than cytotoxic assay
- PCR assay – commercial, automated assay recently become available for detection of toxin B gene in stool samples
  - These assays have good sensitivity (>90%) without loss of specificity (>97%) and the results are available in hours

Table 2. Diagnostic Tests for the Laboratory Confirmation of *Clostridium difficile* Infection

Test	Sensitivity (%)	Specificity (%)	Time to Results
Anaerobic stool culture for *C. difficile*	>90	80-90	2-3 days
Anaerobic stool culture and detection of toxigenic *C. difficile*	>90	>95	3-4 days
Cytotoxin assay (to detect toxin B)	75-85	>97	2-3 days
Enzyme immunoassay (to detect toxins A and B)	70-85	~95	Hours
Glutamate dehydrogenase assay	60-85	85-95	Hours
Polymerase chain reaction (to detect toxin B gene)	490	>97	Hours

Management and Treatment

- Replacement of fluids and electrolytes
- AVOID antiperistaltic drugs and opiates out of concern for toxic megacolon
- DISCONTINUE inciting antibiotic if possible
- Antimicrobial therapy if inciting antibiotic therapy cannot be discontinued or symptoms are persistent or significant
- Mean time to resolution of symptoms with antimicrobial therapy is 3 to 6 days

Table 3. Treatment of *Clostridium difficile* Infection

Indication	Treatment
Mild *C. difficile* infection	Discontinue inciting antibiotic(s), if feasible; metronidazole 250 mg orally every 6 hours for 10–14 days
Severe *C. difficile* infection	Discontinue inciting antibiotic(s), if feasible; vancomycin 125 mg orally every 6 hours for 10–14 days
Fulminant *C. difficile* infection with ileus or toxic megacolon	Metronidazole 500 mg intravenously every 6 hours for 10–14 days and consider vancomycin 500 mg enterally or by enema every 6 hours and surgical consultation
First recurrence of symptomatic infection	Metronidazole or vancomycin as for initial episode (and depending on disease severity)
Subsequent recurrence of symptomatic infection	Vancomycin (prolonged, pulse-dosed, and tapering course)z

Prevention and Control of *C. difficile* Infection in Long-Term Care Facilities (LTCFs)

Table 4. Measures Recommended to Reduce the Risk of *Clostridium difficile* Acquisition and Transmission in Long-Term Care Facilities (LTCFs)4

Surveillance and diagnosis
•Surveillance for *C. difficile* infection should be done in LTCFs.
• LTCFs should have access to laboratory facilities capable of timely and accurate diagnosis of *C. difficile* infection
•Tests for *C. difficile* or its toxins should be done only on diarrheal (unformed) stool specimens, unless ileus due to *C. difficile* is suspected
•Testing stool specimens for *C. difficile* or its toxins from asymptomatic residents (including “test of cure” after treatment) should not be done, unless part of an epidemiological investigation

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Barrier Precautions
• LTCF residents with *C. difficile*-associated diarrhea, especially those with fecal incontinence, should be cared for in a private room, if possible, until the diarrhea has resolved. Dedicated toilet facilities or commode are also recommended.
• Hand hygiene with soap and water or with an alcohol-based product should be done after contact with *C. difficile*-infected residents, their body substances, or their potentially contaminated environment in the LTCF. Handwashing with soap and water is preferred if there is a *C. difficile* outbreak in the facility or if hands are grossly soiled with fecal material
•Healthcare providers should wear gloves for contact with LTCF-residents with *C. difficile*-associated diarrhea and for contact with their body substances or their environment. Gloves should be removed and hand hygiene performed after contact with an infected resident.
•Healthcare providers should wear a gown for contact with an infected resident or when entering the room of an infected resident.
•For residents with *C. difficile* infection, patient care items and equipment (e.g. stethoscopes, BP cuffs) should be dedicated and not shared with other residents. If these items must be shared, they should be carefully cleaned and disinfected between residents.

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Environmental cleaning and disinfection
• The inanimate environment (room surfaces, “high touch” objects, commodes, medical equipment) of LTCF residents with *C. difficile* infection should be carefully cleaned and disinfected using a sporicidal agent (e.g. diluted hypochlorite solution)
Antimicrobial use and other measures
•There should be policies in the LTCF for the judicious use of antimicrobial agents.
•Healthcare providers in the LTCF should be educated about the transmission, clinical features, diagnosis, management, and prevention of *C. difficile* infection.