Clostridium difficile: Some Routine but Controversial Considerations

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Learning Objectives

1. Compare diagnostic tests for *Clostridium difficile* detection.
2. Discuss how to determine resolution of *Clostridium difficile* infection.

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Clostridium difficile

- Ubiquitous organism – soil, water, everywhere
- Spore-forming – spores resistant to drying, lack of oxygen, temperature extremes, alcohol rub
- Toxigenic and non-toxigenic strains
- Glucosyltransferase toxins TcdA and TcdB
- Toxins produced in gastrointestinal lumen

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Clostridium difficile

- Responsible for 25% of antibiotic-associated diarrhea
- Disruption of normal GI microbiome leads to colonization and disease from *C. difficile*
- 21% of asymptomatic patients have colonization with *C.difficile* in their stools
- High rate of colonization in infants
- NAP1/BI/027 strain virulent, caused outbreaks

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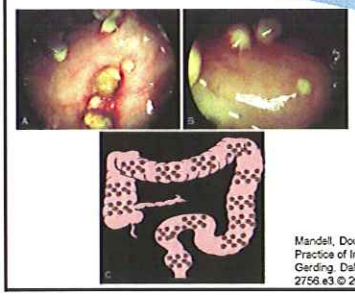
Clinical Presentation



- Fever, diarrhea, abdominal pain
- Mild to Severe disease
- Pseudomembranous colitis
- Complications: megacolon, perforation, shock

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Clostridium difficile Epidemiology

- 250,000 cases treated in US hospitals annually
- 5-10 *Clostridium difficile* infection (CDI) cases per 10,000 patient-days of care
- 14,000 deaths annually
- 25% of cases followed by recurrence
- Attributable mortality 5-10%

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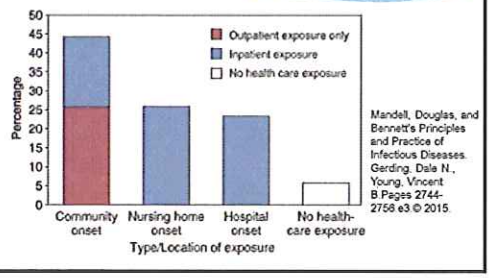
Clostridium difficile Epidemiology



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Diagnosis

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When to Suspect

Diarrhea in the presence of risk factors:

- Any antibiotic versus no antibiotic:
  - Number of antibiotics (risk increases with number)
  - Days of antibiotics (increased risk with increased days)
- Type of antibiotic:
  - *Highest risk*: clindamycin, fluoroquinolones, cephalosporins of second generation and higher
  - *Moderate risk*: penicillins, macrolides, penicillin β-lactamase inhibitors, carbapenems, vancomycin, metronidazole
  - *Lower risk*: aminoglycosides, tetracyclines, trimethoprim, sulfonamides, rifampin
- Proton-pump inhibitors and histamine type 2 blockers
- Patient age (increased risk with age of the patient)
- Prior hospitalization
- Severity of underlying illness
- Abdominal surgery
- Nasogastric tube
- Duration of hospitalization
- Long-term care residency

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Diagnosis

Based on

- Clinical symptoms (usually defined as more than three watery, loose or unformed stools within ≤24 hours), AND
- Positive diagnostic test (usually of a stool specimen) that detects the presence of either the *C. difficile* organism or its toxin genes or *C. difficile* toxin, OR
- Direct visualization of pseudomembranes in the colon by lower gastrointestinal endoscopy

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Diagnosis

5% of patients with severe CDI have obstipation

Diagnosis based on radiologic finding of toxic megacolon and confirmed by lower GI endoscopic visualization of pseudomembranes

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Diagnostic Tests

TEST	SENSITIVITY (%)	SPECIFICITY (%)	COMMENT
Colon endoscopy	~50	100	Sensitivity and specificity are for detection of PMC
Cell cytotoxicity	77-86	97-99	Less sensitive of two "gold standards" compared with toxigenic culture
EIA for toxins A and B	67-92, 60-89	93-99, 93-99	Versus cell cytotoxicity Versus toxigenic culture
EIA for GDH	71-100	67-99	Compared with stool culture for *C. difficile*
Toxigenic culture for *C. difficile*	95-100	96-100	The more sensitive of two "gold standards"
Nucleic acid amplification test (PCR and LAMP)	88-100	88-97	Most sensitive rapid single test available but also most expensive
Two-step GDH, Three-step GDH testing	56-90, 83-100	81-97, 93-100	Discrepancy between GDH and toxin test is 13%-15%

Advantages and Disadvantages of Available Diagnostic Tests

Tests performed on liquid stool to ascertain the patient has diarrhea

- EIA: easy to perform; not sensitive enough leading to "c.diff x3"
- PCR: highly sensitive; positive for several weeks even after treatment
- Selective anaerobic culture: by itself, does not differentiate toxigenic vs. non-toxigenic strains; can be performed on non-stool specimens (e.g., environmental cultures in an outbreak setting)

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Public Reporting

- Hospital-wide *C.difficile* positive lab tests reported publically
- Standard Infection Ratio is calculated based on NHSN aggregate data from 2010-2011
- Risk adjustment done for predictors of *C. difficile* infection, including teaching type, facility bed size, facility prevalence rate, and *C. difficile* laboratory test type
- Implication for clinical care: Test early to avoid misclassification as hospital-onset case

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Epidemiologic Definitions

- **Healthcare facility-onset, healthcare facility-associated CDI:** CDI symptom onset more than 3 days after admission to a healthcare facility, with day of admission being day 1
- **Community-onset, healthcare facility-associated CDI:** CDI symptom onset in the community or less than or equal to 3 days from admission, provided symptom onset was less than 4 weeks after the last discharge from a healthcare facility
- **Community-associated CDI:** CDI symptom onset in the community or less than or equal to 3 days after admission to a healthcare facility, provided that symptom onset was more than 12 weeks after the last discharge from a healthcare facility
- **Indeterminate onset CDI:** CDI case patient who does not fit any of the above criteria for an exposure setting (eg, onset in the community greater than 4 weeks but less than 12 weeks after the last discharge from a healthcare facility)
- **Unknown:** Exposure setting cannot be determined because of lack of available data
- **Recurrent CDI:** An episode of CDI that occurs less than or equal to 8 weeks after the onset of a previous episode, provided that CDI symptoms from the earlier episode resolved

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Testing During Outbreaks

- Testing Patients vs. Environment
- Testing asymptomatic patients, a.k.a., performing active screening cultures not indicated
- Toxigenic cultures may be needed to identify transmission
- Environmental cultures identify contamination of hospital environment

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Clinical Resolution

Determination of Clinical Resolution

- Resolution of diarrhea
- Challenging in critically ill patients because of several other reasons for diarrhea
- Factor in other clinical symptoms and signs – wbc count, stool wbc, abdominal pain

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Test of Cure?

- No test of cure available
- PCR testing not to be repeated within 1 week of previous test

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Risk Factors for Recurrence

- Any prior episodes of *C. difficile* infection
- Antibiotic use (concomitant and/or post– *C. difficile* infection treatment)
- Advanced age
- Prolonged or recent stay in health care facility
- High severity of Horn's index for underlying illness
- Proton-pump inhibitor use
- Infection with NAP1/BI/027 strain type
- Absence of an antitoxin A antibody response

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Summary

- CDI a major public health burden
- Diagnostic testing driven by symptoms
- PCR has several advantages, but costly
- No lab 'test of cure' available

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Learning Assessment

- Which of the following statements regarding diagnostic methods for *Clostridium difficile* infections is accurate?

A. Enzyme immunoassay (EIA) can detect both toxigenic and non-toxigenic strains of *C. difficile*

B. Enzyme immunoassay (EIA) is the most sensitive and specific diagnostic method for *C. difficile*

C. Polymerase chain reaction detects the presence of toxins A and B and is highly sensitive and specific

D. Selective anaerobic culture alone can distinguish between toxigenic and non-toxigenic strains of *C. difficile*

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Thank You!