Detecting *Clostridium difficile*: Is There Light at the End of the Colon?

Dr. Stephen M. Brecher, VA Boston Health Care System

Broadcast live from APIC C. difficile Consensus Conference, Baltimore (www.apic.org)

Detecting C. difficile Is There Light at the End of the Colon?

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The opinions expressed in this presentation are those of the presenter and do not necessarily represent the views of the Veterans Affairs HealthCare System

I have no financial disclosures relevant to this presentation

However, no reasonable offers refused
Have microscope, will travel

Historical Perspective

- ***Bacillus difficilis* (now *C. difficile*) was cultured from healthy neonates in 1935[1]**
- **In the 1960's it was noted that patients on antibiotics developed diarrhea[2]**
  - **"Staphylococcal Colitis"**
    - **Originally thought to be caused by *S. aureus* and treated with oral bacitracin**
    - **Stool cultures routinely ordered for *S. aureus***
- **Early 1970's, a new explanation**
  - **"Clindamycin Colitis"**
    - **Severe diarrhea, pseudomembrane colitis, and occasional deaths documented in patients on clindamycin**

1. **Hall, J.C. and O'Toole E. 1935. Am J Dis Child. 49: 390-402**
2. **Gorbach S.L. 1999. NEJM.341: 1689-1691**

"Antibiotic Associated Pseudomembranous Colitis Due to Toxin-Producing Bacteria"[1]

- **In 1978, *C. difficile* was shown to be the cause of many cases of hospital/antibiotic-associated diarrhea**
- **Bartlett and co-workers demonstrated cytotoxicity in tissue culture and enterocolitis in Syrian Hamsters with stool isolates of *C. difficile* isolated originally from patients with pseudomembranous colitis**

1. **Bartlett, J.G. et al. 1978. NEJM. 298: 531-534**

Factors That Complicated the Discovery of CDI

- *C. difficile* is found in healthy infants who appear to be refractile to CDI[1]
  - Infant intestinal cells do not appear to have receptors for toxins A and B
- Antibiotics often cause diarrhea unrelated to *C. difficile* by disrupting the intestinal microbiome
  - You have 10^{14} bacterial cells and 10^{13} human cells
  - The bacterial cells in your intestine are digesting your food and doing good stuff (mostly)
  - They don't like antibiotic visitations

1. Rousseau, C. et al. 2011. J Clin Microbiol. 49: 858

C. difficile Virulence Factors

- Production of Toxins A and B
  - Increased production in certain ribotypes due to deletions in regulatory genes
  - Why does *C. difficile* make these toxins?
- Resistance to non-treatment antibiotics
  - Fluoroquinolones, macrolides, etc.
- Ability to form spores
  - Some ribotypes do this better than others
  - Antibiotics do not kill spores ➔ recurrent disease
  - Environmental spore survival ➔ transmission
- Surface proteins that promote colonization and infection

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Goals of Testing

- Identify cases of CDI and rule out CDI in other patients with diarrhea[1]
- Initiate specific treatment plans for patients with CDI
- Maximize infection control interventions and environmental cleaning in rooms of CDI patients
- Prevent transmission

1. Polage, CR et al. Nosocomial Diarrhea: Evaluation and treatment of causes other than *C. difficile*. Clin Infect Dis 2012. 55: 982-989

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Changing Difficiliology

- It used to be easy
  - Hospitalized patients on antibiotics with diarrhea
  - Bad tests but we didn't know better and repeated them until they were positive (CD x3 or more)
- No longer easy because
  - Community, healthcare associated and nosocomial CDI
  - Risk factors beyond antibiotics
  - Many reasons for diarrhea, particularly, in hospitalized patients

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C. difficile Clinical Picture

- Mild, moderate and severe disease
- Monitor by
  - Number of unformed bowel movements
  - Leukocytosis
  - Creatinine
  - Albumin
  - Lactate
  - Imaging
- 10-25% treatment failures
  - Antibiotics do not kill spores
- 10-25% recurrent infections

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Who to Test

- Persons with ≥ 3 unformed BM within 24 hours with risk factors for CDI
  - WBC, creatinine, albumin, antibiotics, IBD, surgery, and older age (older than me)
- Do not perform tests on everyone with diarrhea
  - Laxatives, tube-feeding, etc.
- Do not perform tests on asymptomatic patients
- Do not get coerced by "Test of Cure" requests
  - Cured patients can carry toxigenic *C. difficile*
  - How many of you have been told "We need 3 negative Cdiffs before we can take your patient"?

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What to Test
The Brecher Guidelines[1]

Only test loose or liquid stool

"If it ain't loose, it's of no use"

Stick test for stool consistency

"If the stick stands, the test is banned
If the stick falls, test them all"

1. Brecher mindfart (an idea that slips out on it's own)

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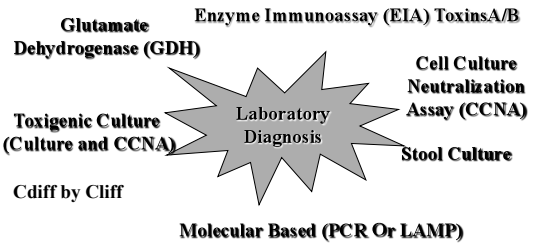
Laboratory Diagnosis of CDI



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CDI Testing Issues

- What is the gold standard?
- Is it time to abandon EIA?
- What about 2-3 step algorithms (difficile dancing)?
- Is PCR/molecular ready for prime time?

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Gold Standard Issues

- All *C. difficile* test assay studies are hard to compare because there is no one reliable, consistently reproducible, consistently used gold standard[1]
- Suggested gold standard has to include a very reliable assay as well as the clinical status of the patient[2]

1. Wilcox, Planche, Fang and Gilligan. Point/counterpoint.JCM.48: 4347-4353.2010
2. Dubberke, E. et al. JCM. 49: 2887-2893. 2011

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Conflicting Results with EIA

EIA Studies[1-6]	
Parameter	Range
Sensitivity	32 – 98.7%
Specificity	84 – 100%
PPV	76.4 – 96%
NPV	88 – 100%

average sensitivity of 60-70%

1. Stamper PD, et al. *J Clin Microbiol.* 2009;47:373-378.
2. Musher DM, et al. *J Clin Microbiol.* 2007;45:2737-2739.
3. Sloan LM, et al. *J Clin Microbiol.* 2008;46:1996-2001.
4. Gilligan PH. *J Clin Microbiol.* 2008;46:1523-1525.
5. Ticehurst JR. *J Clin Microbiol.* 2006;44:1145-1149.
6. Nice review by Planche T, et al. 2008. www.thelancet.com/infection

CDI Testing Issues

Is it time to retire Toxins A/B EIA?

YES

Do not be use as a stand-alone primary assay for the detection of CDI

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CDI Testing Issues

- What is the gold standard?
- Is it time to abandon Toxins A/B EIA?
- What about 2-3 step algorithms (difficile dancing)?
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Glutamate Dehydrogenase

- GDH is a metabolic enzyme that is found in all strains of *C. difficile*
- GDH EIA has
  - High sensitivity (NPV is very high)
  - Low specificity (PPV is low)
    - a + test needs another test (toxin +/- NAAT)
    - Geographical differences in the distribution of certain ribotypes may effect test performance[1]

1. Tenover, F.C. et al. 2010. J. Clin. Microbiol. 48: 3719-3724

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C. Diff Quik Chek Complete

- **Lateral flow EIA for GDH and Toxins A/B on one test card**
  - **Quinn et al[1] reported that if**
    - **Both + = +**
    - **Both - = -**
    - **13.2% discrepant, re-test. Use PCR**
  - **Sharp et al[2] reported that 88% of specimens were both positive or both negative**
    - **Used random access PCR to resolve remaining 12%**

1. Quinn, C. D. 2010. J Clin Microbiol. 48: 603-605
2. Sharp, SE et al. 2010. J Clin Microbiol. 48: 2082-2086

CDI Testing Issues

What about 2-3 step algorithms (difficile dancing)?

A 2-test/1 card EIA for GDH and Toxins A/B with discrepant results resolved by a molecular technique has become a popular alternative to EIA for toxins A/B alone

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CDI Testing Issues

- **What is the gold standard?**
- **Is it time to abandon EIA?**
- **What about 2-3 step algorithms (difficile dancing)?**
- **Is PCR/molecular ready for prime time?**

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FDA Approved PCR Assays for *C. difficile*

Assay	Target Gene	Instrument	TAT (minutes)
BD Gene-Ohm	*tcd*B	Smart Cycler and Amplification or new Automated Version	75-120
Gen-Probe proGastro	*tcd*B	Extraction Smart Cycler/Amp	180-200
Cepheid Xpert	*tcd*B *tcd*C deletion Binary Toxin	GeneXpert	30-45
Great Basin Portrait	*tcd*B	Incubator Ind. Cartridge	90
Focus DX Simplexa	*tcd*B	3M Integrated Cycler	60-90

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FDA Approved Isothermal Amplification-Based Tests for *C. difficile*

Assay	Target Gene	Instrument	TAT (minutes)
Meridian Illumigene	*tcd*A	Inexpensive Incubator/ Reader	45-60
AmpliVue	*tcd*A	Hand Held Disposable	80-90

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Summary of *C. difficile* PCR Published Data

Publication	PCR Assay	Sens/Spec
Chapin, 2011[1]	3 molecular methods	88.5-96.2%/91.6-100%
Noren, 2011[2]	Illumigene (LAMP)	98%/98.%
Kvach, 2010[3]	BD GeneOhm	91.4%/100%
Novak-Weekley, 2010[4]	Cepheid Xpert	94.4%/96.3%
Swindells, 2010[5]	Cepheid Xpert BD GeneOhm	100%/99.2% 94.4%/99.2%
Deshpande[6] (1995-2010)	Meta-Analysis 19 studies	90%/96%
O'Horo[7]	Meta-Analysis 25 studies	92%/94%

1. Chapin KC, et al. *JMD*. 2011;13:395-400.
2. Noren T, et al. *J Clin Microbiol.* 2011;49:710-711.
3. Kvach EJ, et al. *J Clin Microbiol.* 2010;48:109-114.
4. Novak-Weekley, et al. *J Clin Microbiol*. 2010;48:889-893.
5. Swindells J, et al. *J Clin Microbiol*. 2010;48:606-608.
6. Deshpande, A. et al. CID. 2011.53: e81-e90.
7. O'Horo JC et al. Mayo Clin Proc. 2012. 87: 643-651

Quotes from 3 Recent Publications Summarize the Current Issues

1. "…This 2-step protocol, which is now used in National Health Service Laboratories in England, comprises an EIA for GDH detection or NAAT's for toxin gene detection, followed by a relatively sensitive EIA"…Wilcox, MH. 2012. Clin Microbiol Infect. 18 (suppl. 6): 13-20
2. "Performing PCR instead of GDH/EIA/CCN is associated with a >50% increase in CDI incidence rate"…Longtin, Y. et al. 2013. CID.56: 67-73
3. "These data demonstrate that toxin EIA performs poorly both for patients with severe CDI and for those with mild CDI and support the routine use of NAAT for the diagnosis of CDI. The presence of stool toxin measured by EIA does not correlate with disease severity"…Humphries, RM et al. 2013. J Clin Microbiol. 51: 869-873

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CDI Testing Issues

Is PCR/molecular ready for prime time?

YES

BUT (and a Big Butt)
Molecular and Multi-Step Tests Cost More

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Cost vs Value

- Cost is of little value if the results are inaccurate
  - Low sensitivity
  - Low specificity
  - Repeat testing
- Value is measured by impact of the test result on the patient and the facility
  - Increased sensitivity
  - Increased specificity
  - Increased productivity
  - Improved patient care

The most expensive test is one that does not work

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Mural Dyslexia

- "The new tests are more expensive. Our hospital will not let us switch"
- Change requires a business plan, relevant education and a "gate-keeper"
  - The business plan shows that with an accurate method and strict specimen requirements, test volume will decrease
    - Boston VA HCS 4000 to 1400 tests
    - Correct diagnosis, appropriate treatment, and early IC intervention reduce LOS and other costs
  - The gate keeper enforces the guidelines
    - 1 test/patient/week
    - Rejects inappropriate specimens
  - The educational plan
    - Effectively communicates changes to appropriate staff

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One More Problem Do Not Panic

- There is a consequence of improved detection of CDI
- The number of detected cases increase
  - This is not an outbreak
  - It is a breakthrough

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Test Selection Influences Incidence of CDI[1]

- Compared Cell Culture Neutralization (CCN), Xpert *C. difficile* and Illumigene
- Resolution by toxigenic culture
- 200 prospective adult unformed stool samples
  - CCN 23 + (10.5%)
  - Illumigene 35 + (17.5%)
  - Xpert 43 + (21.5%)
- Incidence of CDI nearly doubled with improved assay
- What are the costs (to hospital, to patient, to IC) of missing 50% of CDI cases?

1. Pancholi, P. et al. 2012. J Clin Microbiol. 50:1331-1335

Test Selection Influences Incidence of CDI[1]

- In a large NY cancer hospital, PCR was compared to GDH/CCN
- "In patients with clinical indications for CDI testing, PCR increased the yield *of C. difficile* cases by 2-fold compared to the results with the cytotoxin assay, and this increase was most significant for non-NAP1 strains."

1.Kaltsas, A. et al. 2012. J Clin Microbiol. 50: 1303-1307

Increased Detection Not an Outbreak

- Compared PCR to a 3 step algorithm
  - BD GeneOhm PCR for toxin B gene
  - GDH (Diff-Chek-60, then EIA for Toxins A/B (Quik-Chek) then Cell Culture Neutralization (Vero cells)
- Cases as defined by diarrhea or histopathology/direct visualization

Results for nosocomial cases

PCR	85 positives
3-Step	56 positives

Positives increased by >50%

- 29 cases of CDI were there but not be detected by by a 3-step assay

Longtin, Y. et al. 2013. CID.56: 67-73

Impact of Clinical Symptoms on Interpretation of Diagnostic Assays for CDI[1]

- Compared 8 methods and 2 "gold-standards" with and without clinical symptoms in 150 patients
  - TC & CSD 35 Positives
  - TC & No CSD 44 Positives
  - 4 + assays & CSD 40 Positives
  - 4+ assays & No CSD 50 Positives
- 20 % of patients had laxatives
- 36% did not have clinically significant diarrhea

1. Dubberke, E. et al. 2011. J Clin Microbiol. 49: 2887-2893

If the First PCR is Negative Should I Order Another PCR?

- Of 406 tests from 293 patients with a prior negative PCR[1]
  - 396 negative
  - 10 positive
    - Only 3+ in <7 days
- Exceptions
  - Severe clinical changes

1. Luo RF, Banaei N. *J Clin Microbiol.* 2010;48:3738-3742.

Do We Need to Test for the "Hypervirulent" Ribotype?

- NAP1/B1/027 is often more difficult to treat and can have higher treatment failures and relapse rates[1-3]
- Should we treat patients based on symptoms and severity of disease or treat based on the strain type?
  - Only one FDA approved assay can rapidly detect the gene deletion associated with this strain (*tcdC*)
  - Other strains may also be more virulent
- In a recent study of 310 cases of CDI (43 classified as severe), ribotype was not a predictor of severe disease. WBC and albumin were more clinically relevant[4]
- Molecular characterization is a valuable tool for big picture epidemiological investgations[5]

1. Louie TJ, et al. *N Eng J Med*. 2011;364:422-431. 2. Cornely, OA et al. Lancet Infect Dis.2012; 12:281-289. 3. Figueroa, I. et al. 2012. CID; 55: S104-S109, 4. Walk, S.T. et al. 2012. CID. 55: 1661-1668 5. Wilcox, M.H. et al. 2012. CID. 55: 1056-1063

Relapse or New Infection?

- **Is recurrence associated with the same strain or a different strain?**
- **Of patients with second episodes within 8 weeks, 88% (75/85) had the same strain[1]**
- **Of patients with second episodes > 8 weeks, 65% (32/49) had the same strain[1]**
- **Similar results from Figueroa et al[2]**
- **Diarrhea after an initial episode of CDI may not be CDI[3]**

1. Kamboj, M. et al. 2011. Clin Infect Dis.53: 1003-1006
2. Figueroa, I et al. 2012. Clin Infect Dis. 55: S104-S109
3. Polage, CR et al. 2012. Clin Infect Dis. 55: 982-989

Guidelines for the Diagnosis, Treatment, and the Prevention of *Clostridium difficile* infections

From Table 1: Diagnostic Tests

1. **Only stools from patients with diarrhea should be tested**
2. **NAATs for *C. difficile* toxin genes such as PCR are superior to toxins A+B testing as a standard diagnostic test for CDI**
3. **GDH screening tests for *C. difficile* can be used in 2-3 step screening algorithms with subsequent toxin A+B EIA testing, but the sensitivity of such strategies is lower than NAATs**
4. **Repeat testing should be discouraged**
5. **Testing for cure should not be done**

Am J Gastroenterol advance online publication. 26 February 2013; doi:10.1038/ajg.2013.4

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Recommendations 2013

- Acceptable strategies
  - EIA for GDH/toxins A/B with a molecular assay for discrepant results
  - A molecular test with or w/o a confirmatory toxin assay
- Unacceptable
  - A stand-alone EIA for toxins A/B

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Create Team CDIFF

- **Members**
  - **ID physician, IC guru, GI physician, microbiologist, pharmacist, building management specialist, hospital administrator, ?Cliff**
- **Mission**
  - **Communication and education for value effective test strategies, CD transmission control, and antibiotic stewardship**

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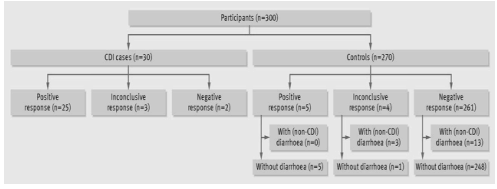
A Sniff by Cliff Will Detect Cdiff

Diagnostic accuracy of dog (Cliff) for detecting *Clostridium difficile* infection (CDI)



Cliff detected 50+ stool samples correctly
Cliff detected 50- stool samples correctly
Nurses did not smell as well (3 studies)

Bomers M K et al. BMJ 2012;345:bmj.e7396

BMJ

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"Creatures"

- **1700 We have creatures on us**
- **1890 Creatures cause disease**
- **1970 Not all creatures cause disease**
- **2000 Some creatures are beneficial**
- **2013 Creatures cure disease (NEJM)**

  "Intestinal Repoopulation: The only time you should take crap from a spouse"

Irony of it all: Detect with dog, treat with poop

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Summary and Conclusions

- ***C. difficile* testing has improved dramatically in the past 3 years**
- **Practice Value-effective rather Cost-effective testing**
- **Limit testing to at-risk patients with clinically significant diarrhea**
- **Eliminate repeat testing unless clinically necessary**
- **Do not perform a test of cure**
- **Create a CDI Team**
- **I see the light…. at the end of the colon**

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