Clinical Impact of Molecular Testing for *C. difficile* Diagnosis

There's Good News and Bad!

Karen C Carroll, M.D.
Professor of Pathology and Medicine
The Johns Hopkins University School of Medicine

JOHNS HOPKINS
MEDICINE

Objectives

After attending this session, participants will be able to:

- Know the features and performance characteristics of the various molecular tests available for the diagnosis of *C. difficile*
- Gain insight on the impact of molecular testing on hospital epidemiology and antimicrobial management

Importance of *Clostridium difficile*

- Most common cause of healthcare associated diarrhea
  - Incidence has more than doubled since 1999 in the USA and Europe
  - Hospital outbreaks are common
  - Estimated costs USA: ~ $1.3 billion annually
- *C. difficile* associated mortality has increased 5-fold since 2000
  - Enhanced virulence—ribotype 027/NAP-1/BI
  - Increased antibiotic resistance of *C. difficile* strains
  - Increasing host vulnerability

DuPont HL. 2011. *N Engl J Med* 364; 463; McGlone SM et al. 2012. *Clin. Microbiol. Infect.* 18:282. MMWR 2012;61:157; Hall AJ, et al 2012. *Clin Infect Dis* 55:216; Weigand PN et al. 2012. J Hosp Infect. 81: 1.

JOHNS HOPKINS MEDICINE

Conundrums of Diagnostic Testing for *Clostridium difficile*

- Rapid and accurate diagnostic tests are considered essential for:
  - Improving patient outcomes
  - Reducing horizontal transmission
- Studies have shown that laboratory results have not impacted treatment decisions
- Uncertainty of test results have led to poor practices
  - Multiple test algorithms
  - Repeat testing
- The optimum method for diagnosis is still a matter of debate: all current methods have limitations

Kufelnicka AM 2012. *Clin Infect Dis* 52:1451;

JOHNS HOPKINS MEDICINE

Various Test Methods for *C difficile* Performance Characteristics

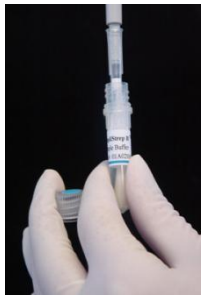
Method/Assays	Performance Characteristics	
	Sensitivity (%)	Specificity (%)
Toxigenic Anaerobic Culture	N/A	N/A
Enzyme immunoassays	31-82	84-100
Cell culture cytotoxin neutralization assays	67-86	97-100
Glutamate dehydrogenase	71-100	76-98
Nucleic acid amplification tests	77-100	93-100

Data derived from Carroll KC and Bartlett JG. 2011. *Ann Rev Microbiology* 65:501-21.

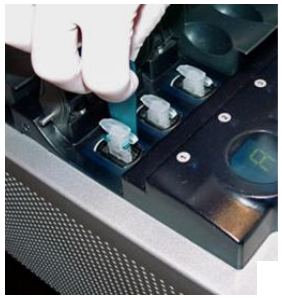
JOHNS HOPKINS MEDICINE

Six FDA-Cleared NAATs for *C difficile* Detection

BD GeneOhm C diff Assay



Lysis - DNA Extraction



Real-time PCR Analysis on the SmartCycler®

Prodesse ProGastro CD Assay

bioMerieux NucliSENS easyMag

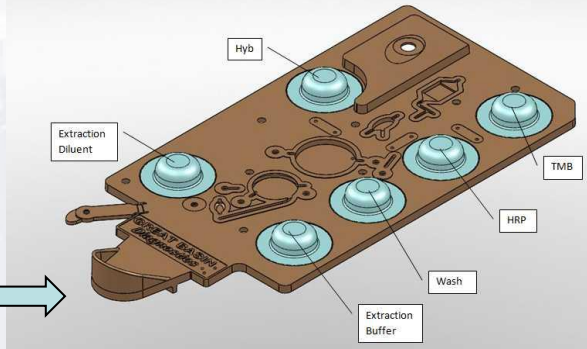
Meridian *illumigene*™

Cepheid GeneXpert Cdiff

3M Integrated Cycler

Focus Technologies Simplexa® C difficile

Portrait Analyzer Toxigenic *C. difficile* assay Great Basin



Available Molecular Assays Summary

Assay	Targets	Extraction	Internal Control	Unresolved rates	TAT	Cost/ test
BD GeneOhm®	*tcd B*	Manual	Yes	0.5-7.0%	75-90 min	$25-$49
Prodesse ProGastro™	*tcd B*	Easy Mag	Yes	2.7%	180 min	$25
Gene Xpert® Cepheid	*tcdB*	Automated (Infinity)	Yes	N/A	29-45 min	$45
Illumigene™ Meridian	*tcdA*	Manual	Yes	0.4-2.9%	70 min	$25-$49
Simplexa® Focus Technologies	*tcdB*	None	Yes	0%	60 min	N/A
Great Basin Portrait	*tcdB*	Automated	Yes	4.5%	70 min	N/A

Current NAATs
Published Performance Characteristics*

Method (# publications)	Sensitivity (% range)	Specificity (% range)	NPV (%range)	PPV (%range)
BD GeneOhm	84-98	91-100	97-100	59-100
ProGastro CD	77.3-100	93.4-100	94.8-100	69.4-100
GeneXpert	94.4-100	93.0-100	97.9-100	72.3-97.8
Illumigene™	83-98	96.6-100	99-100	86.7-100
Simplexa® +	79.6-90.1	93.0-95.8	95.3-98.4	66-81.4
Great Basin+	98.0	90.9	99.5	71.4

*References available upon request + Data obtained from package insert

Xpert® CD/Epi Assay

- Multiplex real-time PCR
- Detects *tcdB*, binary toxin gene *cdt* and *tcdC* deletion at nt 117—markers for 027/NAP1/BI
- Pancholi et al (JCM 2012) –all 027 strains were positive for all 3 markers (n=36)
- Babady et al (JCM 2010)-agreement between Xpert PCR and ribotyping was 93% (42/45)
- Kok, et al (JCM 2011)-false positive results related to non-027 with unusual mutations

JOHNS HOPKINS MEDICINE

NAATs for Diagnosis of *C difficile* Practical Considerations

- NAATs detect genes encoding toxins and not active toxin
  - Will NAATs lead to “over-diagnosis”?
  - Will tests be used appropriately?
- Platforms are expensive
  - Are NAATs cost-effective?
- What is the impact on patient treatment?
- What is the impact on infection control?
  - Will use of NAATs lead to reductions in *C difficile* transmission?

Importance of Clinical Symptoms in Assay Interpretation

Dubberke ER, et al. *J Clin Microbiol* 2011;49:2887

- Evaluation of 8 assays including three NAATs
- Prospective patient interviews/ physical exam
  - Symptoms—abd. pain; diarrhea
  - Demographic data
  - Comorbidities
  - Laxative use within 48h
- Analysis:4 reference stds.
- Std A—Pt. with significant diarrhea and toxigenic *C difficile* recovered from stool
- Std B—toxigenic *C difficile* in stool; symptoms ignored
- Std C—Pt. with significant diarrhea and at least 4 pos. tests
- Std D—4 assays positive; symptoms ignored

JOHNS HOPKINS MEDICINE

Results of Dubberke Study

Standard A

- Prevalence 11%
- NAATs had higher sensitivity; specificity ≤ 86%
- NPV for all assays > 95%
- PPV for ProSpecT, GDH screen, all 3 NAATS < 50%

Standards B,C, D

- Sensitivity did not change or decreased
- Specificity, PPV for all assays increased when clinical symptoms were ignored

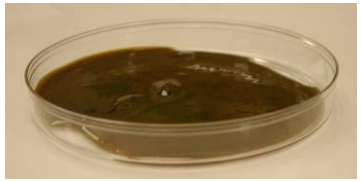
20% of patients were on a laxative

36% of patients did not have clinically significant diarrhea

JOHNS HOPKINS MEDICINE

What Can Laboratories Do To Ensure Appropriate Use of NAATs?

- Limit testing to loose or soft stools that take the shape of the container
- Bristol Stool Chart type 6 or 7



Liquid

Soft and takes shape of container

- Discourage repeat testing within 7 days
- Partner with GI and ID physicians
- Educate nursing staff

JOHNS HOPKINS MEDICINE

Nursing Intervention to Improve *C. difficile* Testing and Treatment

Intervention: 15 minute presentation to nursing staff on the definition of *C. difficile* diarrhea and asymptomatic colonization, and approach to patients with laxatives and diarrhea

	Pre-Intervention (n=120)	Post-Intervention (n=117)	Dubberke *et al.* (n=150)
≥ 3 stools on day of test documented	60 (50%)*	83 (71%)*	NA
Met clinical criteria for CDI	100 (83%)	101 (86%)	96 (64%)
Laxative received within prior 48 hours	53 (44%)	24 (21%)	28 (19%)

*Based on documentation by nursing in the medical record

Courtesy of Sara Cosgrove, MD and Whitney Redding, PharmD
Unpublished data

JOHNS HOPKINS MEDICINE

Dubberke et al. *J Clin Microbiol* 2011;49(8):2887-93.

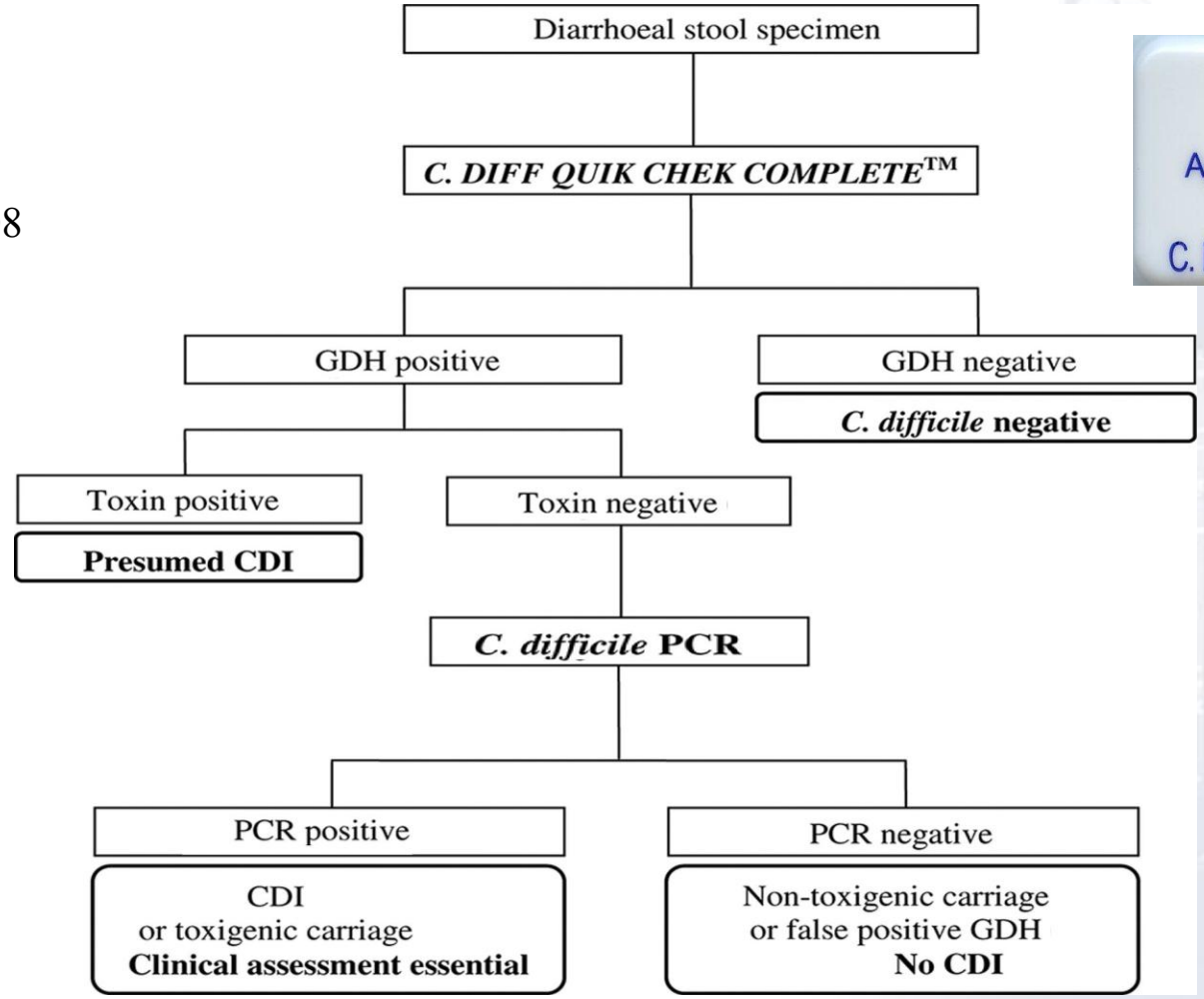
Cost of NAATs

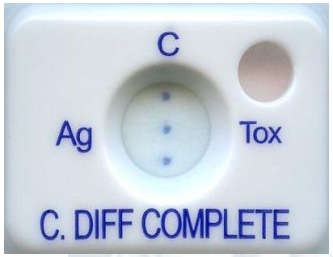
- Equipment expenses
- Labor—depending on assay and volume of testing
- Reagents—on average 2-3 times the costs of EIAs

JOHNS HOPKINS MEDICINE

3-Step Algorithms

Modified from
Swindells, et al
JCM 2010;48:608





JOHNS HOPKINS MEDICINE

Laboratory Cost-Effectiveness Analyses

Study	Algorithm/ Comparator	Same day Report	Cost per positive US $	Cost per test US $
Doing DMID 2010;66:129	GDH + PCR PCR alone	100%	N/A	71.00 38.00
Larson JCM 2010;48:124	GDH + toxin EIA GDH + PCR GDH + toxin EIA + PCR		486 425 368	18.05 35.22 40.68
Sharp JCM 2010;48:2082	GDH + EIA + PCR PCR alone	100%	N/A	11.50 (88%) 44.88 (12%) 33.38

JOHNS HOPKINS MEDICINE

Potential Disadvantages to Multi-Step Algorithms

- Time to detection—Impact on patient care?

Sydnor ERM, et al. 2011. Antimicrobial prescribing practices associated with *Clostridium difficile* testing. *ICHE* 32:1133.

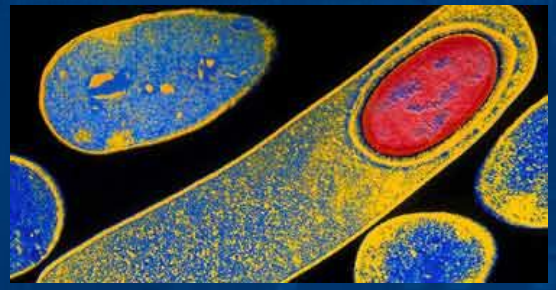
- Maintenance of multiple test methods
- Cost/re-imbursement issues
- Variability in reported GDH assay performance

Tenover FC, et al. 2010. Impact of strain type on detection of *C. difficile:* Comparison of molecular diagnostic and EIA approaches. *J. Clin. Microbiol*. 48:3719-24.

Carroll KC and Loeffelholz M. 2011. Conventional vs. Molecular Methods for the Detection of *Clostridium difficile. J. Clin. Microbiol* 49:S49-S52.

JOHNS HOPKINS MEDICINE

Impact of NAATs on Infection Control



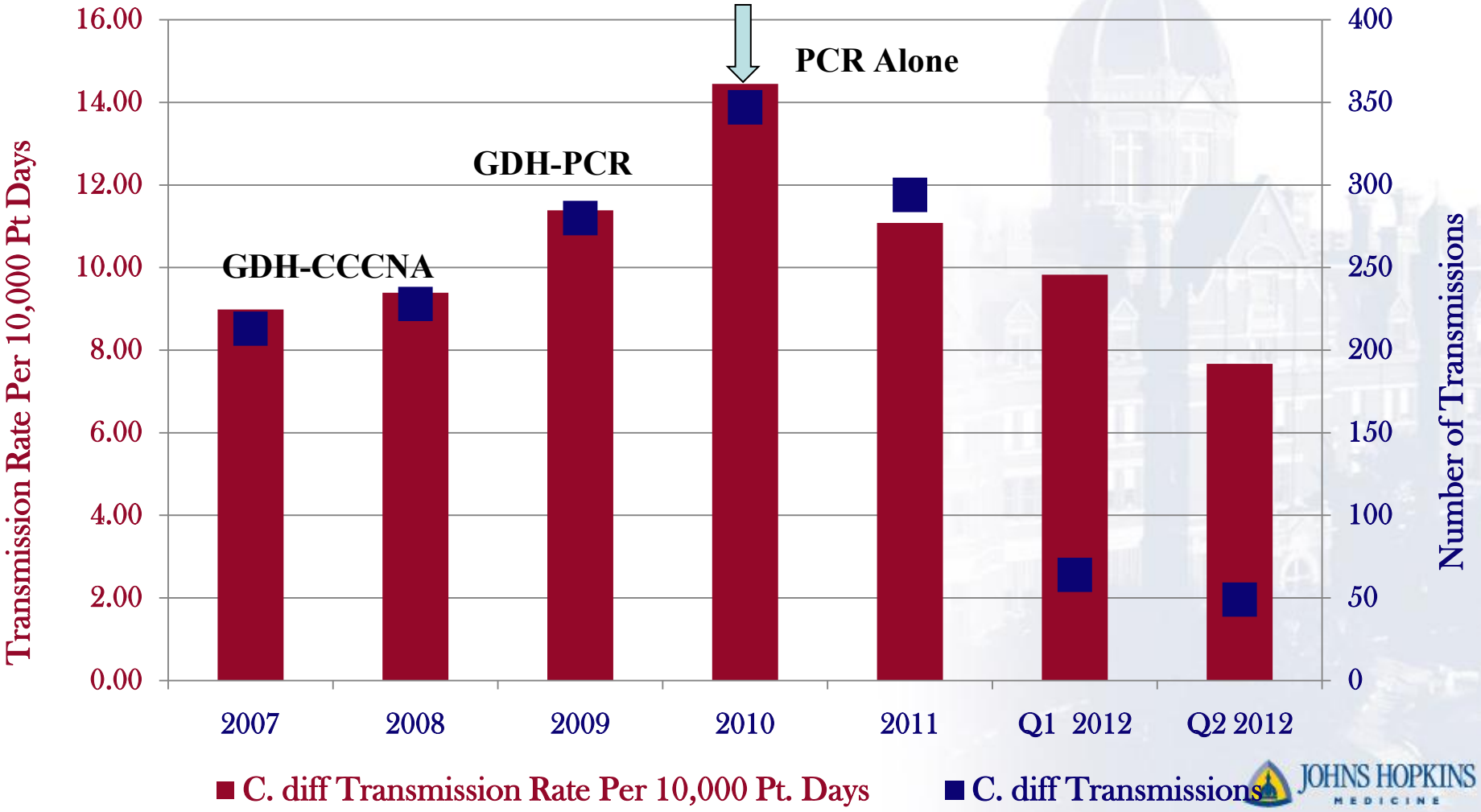
JOHNS HOPKINS
MEDICINE

Impact of Molecular Testing on *C difficile* Infection Rates

- Several manuscripts report doubling of *C difficile* rates initially when making the switch from EIA to molecular testing algorithm
  - Negative impact on public health reporting if method of testing is not considered
  - May be a disincentive to eliminating EIAs
- After period of increase, rates declined, suggesting better case detection leading to decreased transmission

Fong KS et al 2011; ICHE 32:932; Goldenberg SD 2012; ICHE14:1231-32;

C. Diff Transmissions for JHH: 2007 – Q2 2012



JOHNS HOPKINS MEDICINE

Impact of Molecular Testing on Infection Control

Cantanzaro and Cirone. 2011; *Am J Infect Control*

- 6 month retrospective study comparing impact of switch from ToxA/B EIA to PCR
- Practice prior to switch to PCR
  - Pre-emptive isolation of symptomatic patients
  - 3 negative toxin A/B EIA tests required to remove pt. from isolation
- Switch to PCR; pre-emptive isolation until single neg.
- Post implementation significant decrease in:
  - Healthcare associated CDI (4.4 vs. 0.9 /10,000 pt. days, P=.02)
  - Patient isolation days (1,022 vs. 364, P <.00001)
  - Tests ordered (P=.02)
  - Metronidazole Rx for pts. with negative C diff tests (P=.004)

Use of Molecular Assay for Diagnosis of *Clostridium difficile:* Summary

Good News

- Variety of available molecular platforms
- NAATs are the most sensitive methods available
- NAATs provide rapid results
- May be economical
  - Eliminate need for retesting
  - May reduce transmission
  - Remove patients from isolation more quickly
  - Reduce unnecessary treatment

Bad News

- Molecular assays are 2x the cost of other methods
- Specificity, PPV are poor if not used appropriately
- NAATs may increase *C difficile* rates-impact public reporting

JOHNS HOPKINS MEDICINE

Acknowledgements

- Sara Cosgrove, MD
- Lisa Maragakis, MD
- Whitney Redding, PharmD
- JHH *C difficile* Research Team

JOHNS HOPKINS MEDICINE