Discovering the Optimal Approach to Diagnosing *Clostridium difficile* Infection (CDI)

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Learning objectives

After this webinar, you will be able to:

- Review the clinical background of C. difficile and its role as a pathogen in human health
- Identify various ways in which C. difficile can be accurately diagnosed
- Discuss the revised treatment recommendations for C. difficile
- Evaluate the role of the 2018 modifications to the NHSN reporting criteria for healthcare-associated C. difficile

Clostridium difficile infection (CDI)

- Gram-positive, spore forming anaerobic bacillus
- First linked to disease in 1978
- Frequently causes diarrheal illness in hospitalized patients, patients with IBD or those treated with Abx
- Causes wide range of illness
  - Diarrhea
  - Pseudomembranous colitis
  - Toxic megacolon
  - Systemic symptoms: fever, nausea, malaise, anorexia
- New research shows
  - Decreasing effectiveness of metronidazole therapy
    - 50% success with single course of treatment
    - 2 clones of metronidazole resistant *C. difficile*
- Part of the GI Flora in
  - 1-3% of healthy adult
  - 70% of children < 12 months

The financial and human impact of *C. difficile*

	Number of annual cases	Cost	Number of annual deaths
Hospital – onset, hospital acquired (HO-HA)	165,000	$1.3 B	9,000
Community-onset hospital acquired (CO-HA) [4 weeks of hospitalization]	50,000	$0.3 B	3,000
Nursing home-onset	263,000	$2.2 B	16,500

Number one risk factor for *C. difficile* in healthcare – antibiotics

Very commonly related	Less commonly related	Uncommonly related
Clindamycin Ampicillin Amoxicillin Cephalosporins Fluoroquinolons	Sulfa Macrolides Carbapenems Other penicillins	Aminoglycosides Rifampin Tetracycline Chloramphincol

- 96% of patients with CDI receive ABX within 14 d of symptoms
- 100% of patients receive within 3 months

C. difficile testing methods

- Anaerobic stool culture
  - With testing of recovered isolates for cytotoxin production
- Cell culture cytotoxicitiy assay
- Toxin testing
  - EIA (enzyme-linked immunosorbent assay)
  - Glutamate dehydrogenase (GDH)
- PCR

Anaerobic stool culture (toxigenic culture)

- “Gold standard”
- Specimens can be heated to enhance spore formation before plating
- Specimens plated on specific media
  - Usually cycloserine-cefoxitin-fructose agar +/- horse blood
- Incubated anaerobically
  - For up to 5 days for final negative
- Colony appearance
  - Yellow, spreading
- *C. difficile* isolates recovered for cytotoxin production
  - grown in chopped-meat broth and supernatant passed through filter to determine toxigenicity
  - Supernatant purified and added to shell vials to observe for cytotoxic effect
- Turn around time 5 days or more

Anaerobic stool culture - *C. difficile*

Anaerobic culture (toxigenic culture) sensitivity and specificity

Study	Comparison Method	Sensitivity %	Specificity %	PPV %	NPV %
Peterson, et al.	≥3 positive test results*	100 (85.9-100)	92.9 (88.2-95.9)	68.2 (52.3-80.9	100 (97.5-100)
Stamper, et al.	Used as “gold standard”				
Eastwood, et al.	Used as “gold standard”				

**Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR*

Cell culture cytotoxicity assay

- Cells of specific origin incubated in shell vials with sample (liquid from centrifuged stool) and buffer
  - MRC-5 cells (fetal lung cells)
  - Human foreskin fibroblasts
- Shell vials examined for cytotoxic effect
- Toxin B presence can be confirmed with neutralized cytotoxic activity in a control well containing the antitoxin

Cell culture cytotoxicity sensitivity and specificity

Study	Comparison Method	Sensitivity %	Specificity %	PPV %	NPV %
Peterson, et al.	≥3 positive test results*	90.0 (72.3-97.4)	97.0 (93.2-98.8)	81.8 (63.9-92.4)	98.5 (95.2-99.6)
Stamper, et al.	Toxigenic anaerobic culture	67.2 (55.4-79.0)	99.1 (98.1-100)	93.2 (85.7-99.9)	94.4 (92.0-96.8)
Eastwood, et al.	Toxigenic anaerobic culture	86.4 (79.1-91.9)	99.2 (97.9-99.8)	2% prev-67.7 10% prev-92.0	2% prev-99.7 10% prev-98.5

**Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR*

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Enzyme Immunoassays (EIAs)

- One of the most frequently used diagnostic tests for CDI for past 10 years
- Initially targeted toxin A
- Disease-causing strains producing toxin B alone were identified
- EIAs updated to test for both toxins
- Cost $128 (clinical charge)
- Turn around time 4-6 hours

EIA sensitivity and specificity

Study	Comparison Method	Sensitivity %	Specificity %	PPV %	NPV %
Peterson, et al.	≥3 positive test results	86.7 (68.4-95.6)	98.5 (95.3-99.6)	89.7 (71.5-97.3)	98.0 (94.6-99.4)
Eastwood, et al.	Toxigenic anaerobic culture	60.0-81.6	91.4-99.4	2% prev (16.8-69.0) 10% prev (47.0-92.4)	2% prev (99.3-99.6) 10% prev (95.6-97.9)

**Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR*

Generally accepted sensitivity of EIA 60-70% compared to toxigenic culture

Glutamate Dehydrogenase (GDH)

- “Common antigen” test
- Alternative to traditional EIA-meant to be more sensitive
- Uses EIA or latex agglutination technology
- Sensitivity 69-100%
  - Generally accepted as 80% sensitive
  - 100% sensitivity not using toxigenic culture as gold standard
- Specificity low
- 2 or 3-stage technique (based on presumed high sensitivity)
  - GDH initial test
  - Retest positives with more specific test
    - EIA
    - PCR
- Eastwood et al
  - Sensitivity 87.6%
  - Specificity 94.3%

PCR sensitivity and specificity

Study	Comparison	Sensitivity %	Specificity %	PPV %	NPV %
Peterson, et al.	≥3 positive test results*	100 (85.9-100)	96.5 (92.6-98.4)	81.1 (64.3-91.4)	100 (97.5-100)
Stamper, et al.	Toxigenic anaerobic culture	83.6 (74.3-92.9)	98.2 (96.8-99.6)	89.5 (81.5-97.4)	97.1 (95.3-98.9
Eastwood, et al.	Toxigenic anaerobic culture	88.5 (80.3-93.6)	95.4 (92.9-97.0)	2% prev 28.1 10% prev 68.0	2% prev 99.7 10% prev 98.7

**Peterson study evaluated 4 tests: 1. Anaerobic culture; 2. Cell culture cytotoxicity; 3. EIA; 4. Real-Time PCR*

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C. difficile: An old bug providing contemporary clinical and laboratory challenges

- Persons with ≥ 3 unformed BM within 24 hours with risk factors for CDI (**C**linically **S**ignificant **D**iarrhea)
- ↑ WBC, ↑ creatinine, ↓ albumin, antibiotics, IBD, surgery and older age
- Patients who completed therapy who still have CSD
- Do not perform tests on everyone with diarrhea

  - Consider non-infectious etiologies

Alternative causes of diarrhea in the hospitalized patient

- Careful selection of the patient is important:
  - 20-44% are receiving laxatives
  - 36-50% do not have significant diarrhea
  - tube feeding can cause liquid stools

Dubberke ER, Burnham CA. Diagnosis of Clostridium difficile Infection : Treat the patient, Not the Test. JAMA Intern Med. 2015 Nov;175(11):1801-2.

Who to test

- “Judicious use of *C. difficile* testing is important because a *C. difficile* colonization state exists and can be common.”
- One study showed nearly 50% of hospitalized patients had *C. difficile* in their stool by the end of 4 weeks despite no symptoms of CDI
- Testing should be reserved for patients with ≥3 loose stools per day for at least 1-2 days
- “Stools taking the shape of the container”
- Number of EIA tests is controversial
- Wait 7-14 days between samples from a single patient after positive result and treatment
- Currently requests can be limited to one PCR per 5-7 days

The challenges of *C. difficile* testing

- Incidence and severity of *C. difficile* increasing
- Disease caused by toxin production
  - Diagnostic Challenge, do labs detect toxin versus organism
    - Detection of organism increases sensitivity
    - Detection of toxin increases clinical specificity
- What's the Best Test(s)?

Table 3. Nondiarrheal Outcomes and Treatment by *Clostridium difficile* Test Group

Outcome	*C difficile* Positive		*C difficile* Negative	
	Tox+/PCR+ (n = 131)	Tox−/PCR+ (n = 162)	Tox−/PCR− (n = 1123)	*P* Value[a]
***C difficile*–Related Complication or Death Within 30 d, No. (%)**				
Complication[b]	10 (7.6)	0	3 (0.3)	<.001
Death[c]	11 (8.4)	1 (0.6)	0	<.001
Complication or death	18 (13.7)	1 (0.6)	3 (0.3)	<.001
Repeat *C difficile* Testing Within 14 d, No. (%)				
Retested	14 (10.7)	61 (37.7)	374 (33.3)	<.001
Positive toxin test result	3 (2.3)	13 (8.0)	17 (1.5)	<.001
Repeat *C difficile* Testing at 15-30 d, No. (%)				
Tested	26 (19.8)	18 (11.1)	106 (9.4)	.001
Positive toxin test result	14 (10.7)	5 (3.1)	10 (0.9)	<.001
Treatment Within 14 d				
Metronidazole or oral vancomycin, No. (%)[d]	131 (100)	66 (40.7)	361 (32.1)	<.001
Duration of metronidazole or oral vancomycin, if treated, median (IQR), d	14 (11-14)	6 (3-11)	5 (2-9)	<.001
Non–*C difficile* antibiotic, No. (%)	98 (74.8)	141 (87.0)	912 (81.2)	.03
Duration of non–*C difficile* antibiotic, if treated, median (IQR), d	11 (3-14)	10 (4-14)	10 (4-14)	.13
Treatment at 15-30 d				
Metronidazole or oral vancomycin, No. (%)	75 (57.3)	35 (21.6)	137 (12.2)	<.001
Duration of metronidazole or oral vancomycin, if treated, median (IQR), d	9 (3-14)	4 (3-15)	6 (3-9)	<.001

Polage et al, JAMA Int Med. 2015; 175(11): 1792-1802

Key points

Point-Counterpoint: What Is the Optimal Approach for Detection of *Clostridium difficile* Infection?

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- NAAT-based testing often increases reported CDI infection rates at healthcare institutions
- Performance of any test can be significantly altered based on pre-analytical factors
- NAATs and culture-based methods are more sensitive but less specific than toxin assays, whereas toxin assays are less sensitive but more specific than NAATs
  - We don't know what the best strategy is in relation to sensitivity versus specificity!
- Data suggest that patients testing positive by NAAT without active CDI may be more likely to spread *C. difficile*

J Clin Microbiol. 2017; 55(3): 670-681

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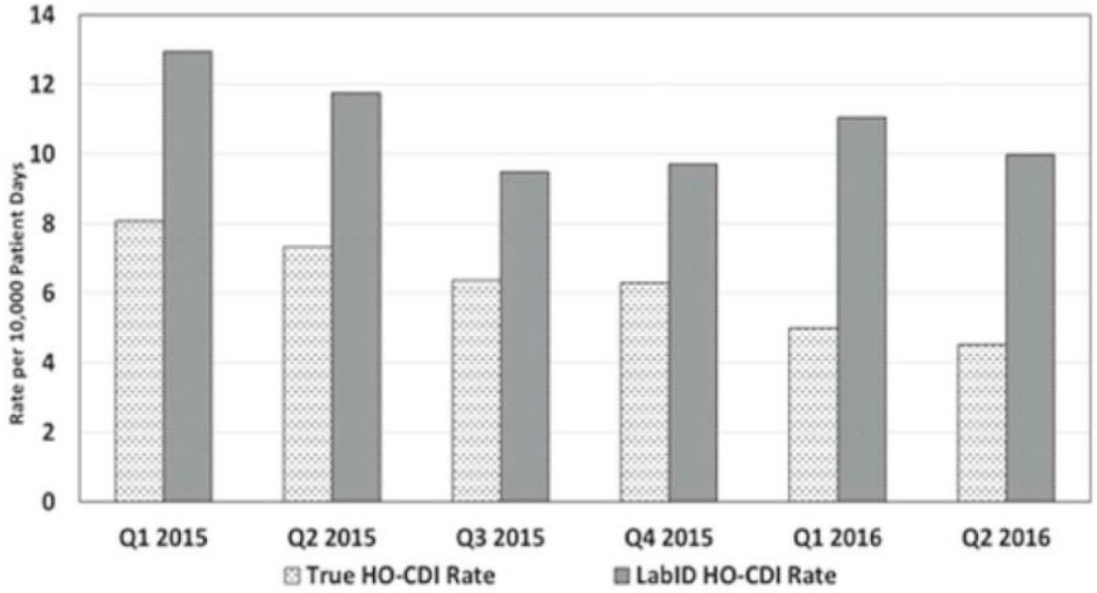
NHSN reporting

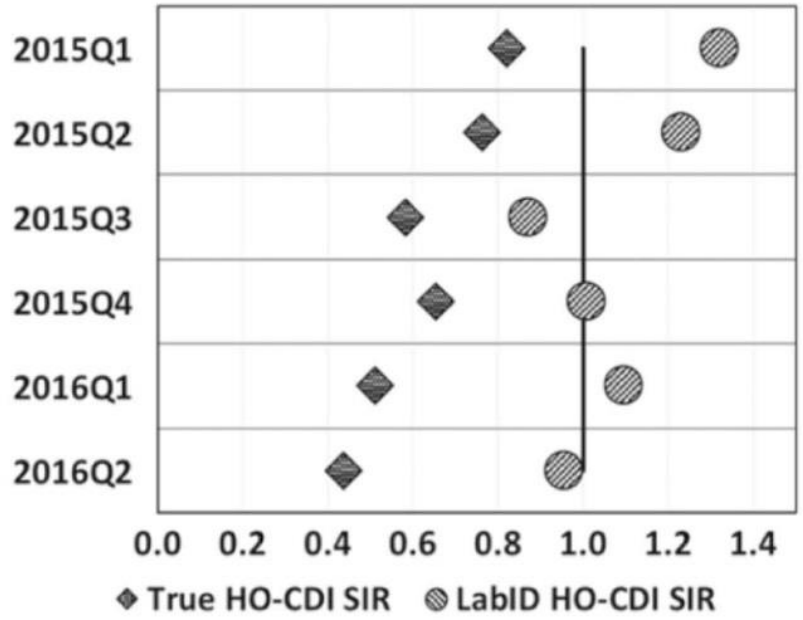
- Facilities may choose to monitor *C. difficile* where *C. difficile* testing in the laboratory is performed routinely only on unformed (specifically, conforming to the shape of the container) stool samples
  - NO CHEATING!! Facilities are allowed to implement active surveillance protocols for epidemiology, but these results should not be reported in NHSN as Community Acquired *C. difficile!*
- All inpatient locations – outpatient locations can be reported, but must be mapped accordingly
- BIG CHANGE FOR 2018
  - When using a multi-testing methodology for CD, the final result of the last test will determine if the CDI positive laboratory assay definition is met.
    - So if using NAAT + toxin testing, only toxin results are reported to NHSN
  - CAUTION – This may change the institution's SIR or Standardized Infection Ratio

The clinical challenges of *C. difficile* testing

a: True HO-CDI Rate vs NHSN LabID HO-CDI Rate



b: True HO-CDI SIR vs NHSN LabID HO-CDI Event SIR



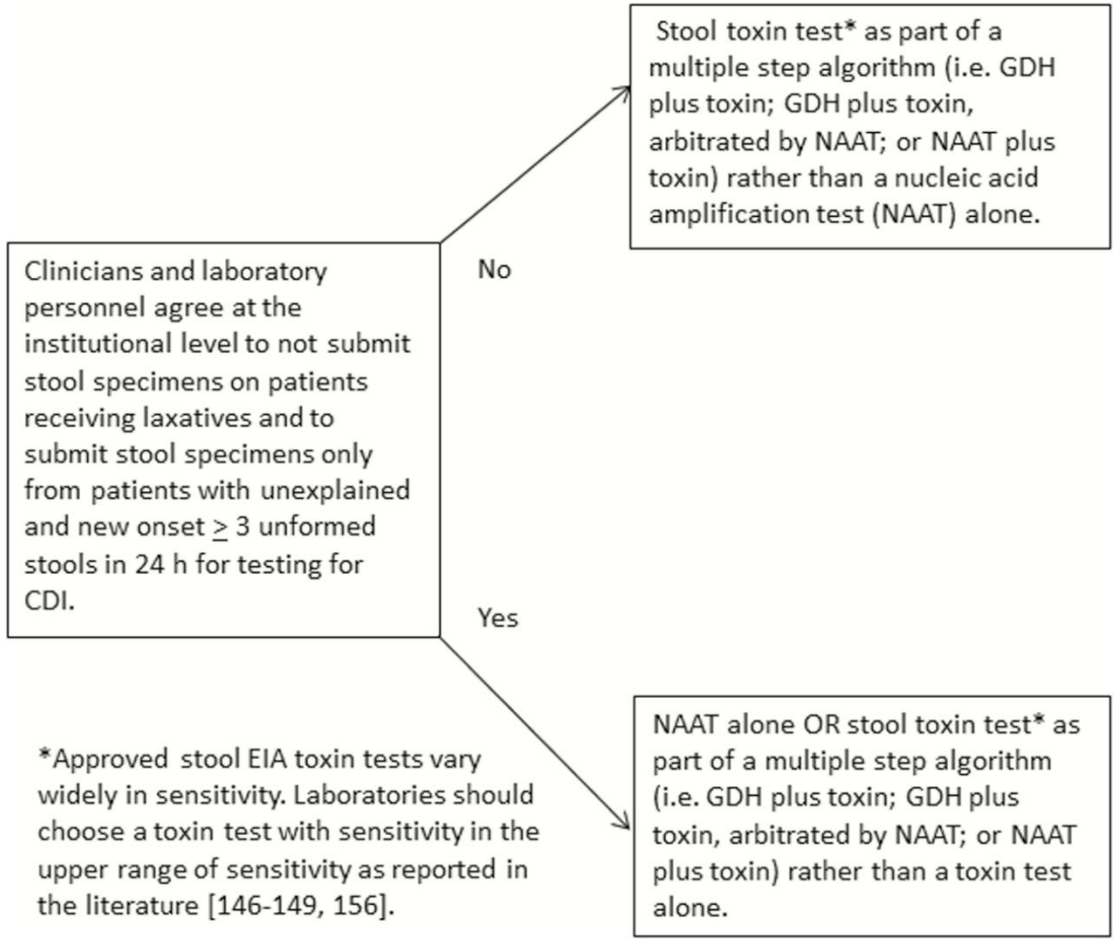
- 490 HO-CDI LabID events during 452,587 patient-days
  - 284 (58%) were true HO-CDI
  - 206 (42%) were classified as nontrue (either inappropriate (90.5%) or delayed testing (9.5%))

Rock et al, Am Jour Infect Control, 2018, In Press

What the guidelines said and did not say

- Shifts in guidance
  - Potential Major Change in Recommended Testing Strategy, but Weak Evidence – Expect Future Updates as New Data Emerges
    - Underscores the need for outcome studies in NAAT+/Toxin Negative Patients
  - Patients with unexplained and new-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI – Weak Evidence
  - Do not perform repeat testing (within 7 days) during the same episode of diarrhea and do not test stool from asymptomatic patients, except for epidemiological studies – Strong Evidence
  - In routine or endemic settings, perform hand hygiene before and after contact of a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand hygiene product
    - Addition of alcohol-based products new, based on weak evidence – MAJOR shift for Infection Prevention

The 2017 IDSA guidelines, lab testing



From: Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)
Clin Infect Dis. Published online February 15, 2018. doi:10.1093/cid/cix1085

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So how should healthcare facilities adopt to this shift?

- First, stop and take a breath!
- This is really test stewardship – We need to provide the right test for the right patient

Test stewardship can work

Fig. 1. Order volume by date.

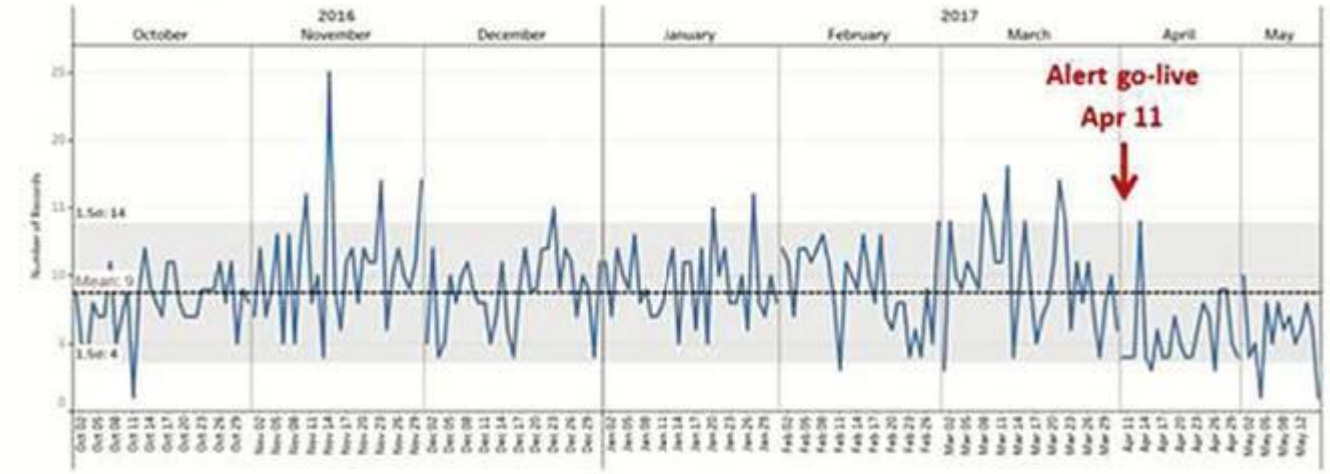
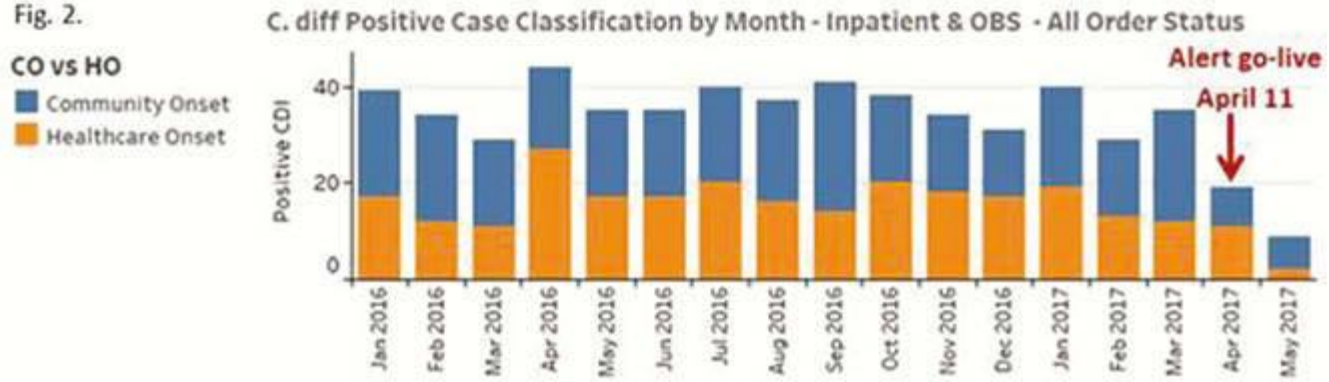


Fig. 2.



- Test Stewardship can reduce ordering
  - Alert versus Hardstop
    - Effectiveness of alert can wane over time
- Alter/Hardstop Values
  - Fires on third day of admission
  - Evaluates for documented diarrhea
  - Evaluates for laxative use
  - Also can consider elevated temperature

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Drees et al. Open Forum Infectious Diseases. 2017; 4(S1)-S1-S2

So how should healthcare facilities adapt to this shift?

- First, stop and take a breath!
- This is really test stewardship – We need to provide the right test for the right patient
- The Lab can Also Help!

It all comes down to the poo….

- Evaluate specimens that arrive in the Lab,
  only accept those specimens that take the form of the transport container
- Establish acceptance criteria
  - Specimens submitted within 7 days of a previous test should not be repeated
    - Some centers have limited testing on patients with a positive NAAT to 14 or 21 d before retesting – Needs Further Study
- Use IT solutions to help
  - Alerts or Best Practice Alerts can help, but “Notification Fatigue” can occur
  - Consider “Hard Stops” that prevent the provider from ordering without providing a reason
  - Consider Including “Mandatory Consultation” with ID or Lab Director if test is flagged as an inappropriate order – Can by difficult, but can improve culture.

So how should healthcare facilities adopt to this shift?

- First, stop and take a breath!
- This is really test stewardship – We need to provide the right test for the right patient
- The Lab can Also Help!
- Use your IT Department to Help
- Education of Physicians and Nurses

	Baseline Period			Intervention Period		
	Positive PCR (n = 40)	Negative PCR (n = 80)	Overall (n = 120)	Positive PCR (n = 74)	Negative PCR (n = 148)	Overall (n = 222)
≥3 stools documented on day of test,[a] No. (%)	18 (45)*	42 (52)	60 (50)[NS]	52 (70)*	48 (32)	90 (45)[NS]
Any laxative within 48 h of test, No. (%)	20 (50)	33 (41)	53 (44)**	14 (19)	46 (31)	60 (27)**
Age (y), median (IQR)	54 (46–71)			59 (47–72)		
Unit, No. (%)						
Floor	27 (68)			53 (72)		
Stepdown	4 (10)			10 (14)		
ICU	9 (23)			11 (15)		
Service, No. (%)						
Medicine	33 (83)			58 (78)		
Surgery	7 (18)			16 (22)		
Concomitant PPI, No. (%)	26 (65)			36 (49)		
Documented clinical rationale for testing,[b] No. (%)	36 (90)			68 (92)[c]		
Treatment Concordance,[d] No. (%)	29 (73)			58 (78)		
Asymptomatic carriage	0/4 (0)			0/9 (0)		
Mild–moderate infection	24/28 (86)			41/46 (89)		
Severe infection	4/7 (57)			14/15 (93)		
Severe complicated infection	1/1 (100)			3/4 (75)		

Buckel et al, ICHE, 2015; 36(2): 217-221

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So how should healthcare facilities adopt to this shift?

- First, stop and take a breath!
- This is really test stewardship – We need to provide the right test for the right patient
- The Lab can Also Help!
- Use your IT Department to Help
- Education of Physicians and Nurses
- Antimicrobial Stewardship

Questions?

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