C. difficile Testing and Diagnostic Stewardship

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9/26/2023

NEBRASKA HOSPITALS

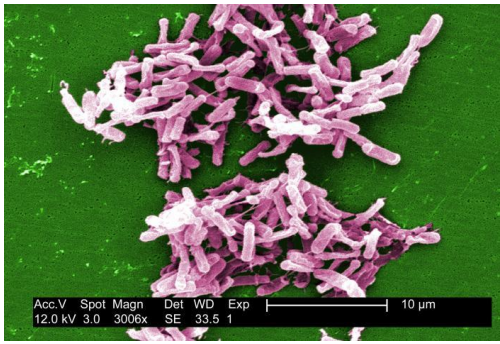
ASAP

Nebraska Antimicrobial Stewardship Assessment and Promotion Program

Disclosures

The presenters have no financial disclosure or conflict of interest with the presented material.

Clostridium difficile Infection (CDI)



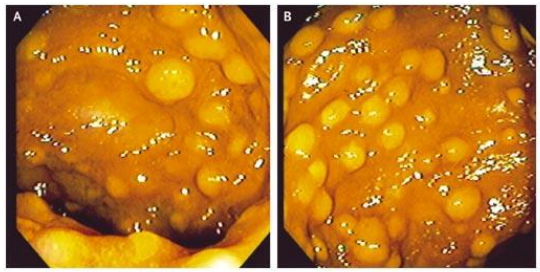
Anaerobic, gram positive, spore forming bacteria

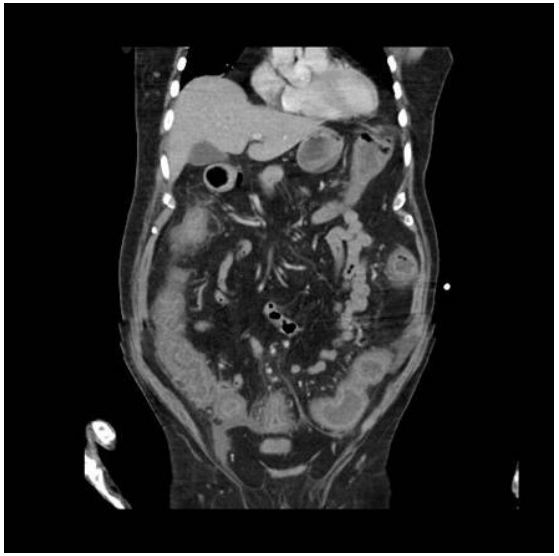
Most common **infectious** cause of nosocomial diarrhea

- Causes <10% or less of hospital onset diarrhea
- Colonization is common 5-20% inpatients

Infection can produce varying illness

- Diarrhea with crampy abdominal pain or distention
- Leukocytosis, fever





C. difficile Diagnosis

Can nurses diagnose by smell?

Survey of 138 nurses at one institution

- Sensitivity 55%
- Specificity 83%
- PPV 35%
- NPV 92%

Nurses were pretty good at ruling it out

Burdette. *Clin Infect Dis*. 2007;44:1142.

Dogs Are Much Better!

Using a dog's superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study

OPEN ACCESS *BMJ*. 2012;345:e7396.

Marije K Bomers *consultant*[1], Michiel A van Agtmael *consultant*[1], Hotsche Luik *canine trainer and psychologist*[2], Merk C van Veen *resident*[3], Christina M J E Vandenbroucke-Grauls *professor*[4], Yvo M Smulders *professor*[1]

C. difficile sniffing dog

- Stool sample sensitivity and specificity 100%
- Detection rounds (N=300)
  - 83% sensitive
  - 98% specific

CDI Diagnosis

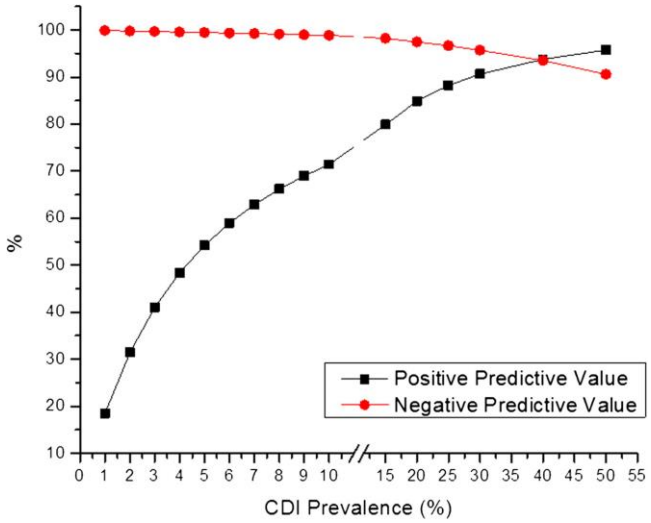
Test	Detects	Time to Report	Cost	Advantages *Disadvantages*
Toxin EIA	Free toxin	Hours	$	Fast, simple, moderate specificity *Poor sensitivity*
GDH (antigen)	Vegetative bacteria	Hours	$	Fast, easy, high sensitivity *Poor specificity, needs toxin assay*
NAAT (PCR)	Toxin gene(s)	Hours	$$$	Fast, high sensitivity *Low to moderate specificity*
Cell culture cytotoxicity neutralization assay*	Free toxin	2 to >3 days	$$	Excellent sensitivity and specificity *Time consuming and complex*
Toxigenic culture*	Vegetative bacteria or spores	2 to >3 days	$$	Excellent sensitivity *Difficult, time consuming, needs toxin assay*

* Gold standards

CDI Testing Key Points

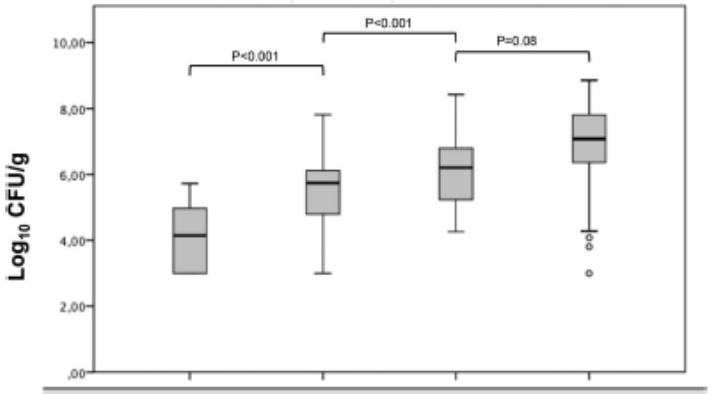
Prevalence of disease has a major impact on test interpretation

Theoretical values of PPV and NPV for increasing CDI prevalence calculated using pooled sensitivity (90%) and specificity (96%) which is that of NAAT



PCR can detect very low levels of CDI: Levels that may not need to be treated but may still contribute to transmission

C. Difficile bacterial loads by test result



Group	1	2	3	4
PCR	+	+	+	+
GDH EIA	-	+	+	+
CCA	-	-	+	n/a
ToxAB EIA	-	-	-	+

Deshpande A. *Clin Infect Dis*. 2011;53:e81-90.
Dionne L, et al. *J Clin Micro*. 2013;51:3624-30.

Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

JAMA Intern Med. 2016;175:1792.

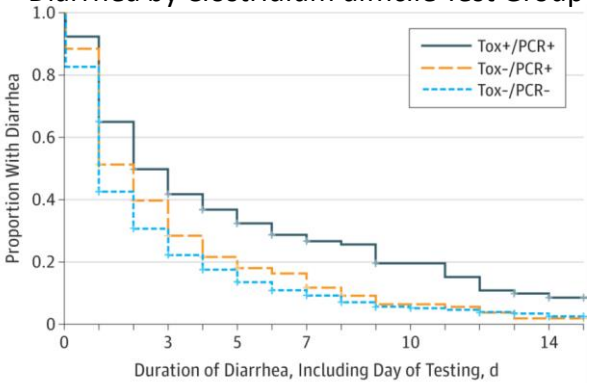
Christopher R. Polage, MD, MAS; Clare E. Gyorke, BS; Michael A. Kennedy, BS; Jhansi L. Leslie, BS; David L. Chin, PhD; Susan Wang, BS; Hien H. Nguyen, MD, MAS; Bin Huang, MD, PhD; Yi-Wei Tang, MD, PhD; Lenora W. Lee, MD; Kyoungmi Kim, PhD; Sandra Taylor, PhD; Patrick S. Romano, MD, MPH; Edward A. Panacek, MD, MPH; Parker B. Goodell, BS, MPH; Jay V. Solnick, MD, PhD; Stuart H. Cohen, MD

1416 inpatients tested for CDI (toxin assay)

- PCR testing without results
- 21% (293/1416) positive by PCR but only 44.7% (131/293) of those positive by toxin assay

- PCR+/Toxin- compared to PCR+/Toxin+
  - Lower CDI bacterial load
  - Less antibiotic exposure
  - Less inflammation
  - Less frequent and shorter duration diarrhea
  - **No CDI related complications**

Kaplan-Meier Curves of Time to Resolution of Diarrhea by Clostridium difficile Test Group



No. at risk

Tox+/PCR+	131	62	41	29	25	8
Tox-/PCR+	162	60	29	21	10	2
Tox-/PCR-	1123	328	172	99	42	23

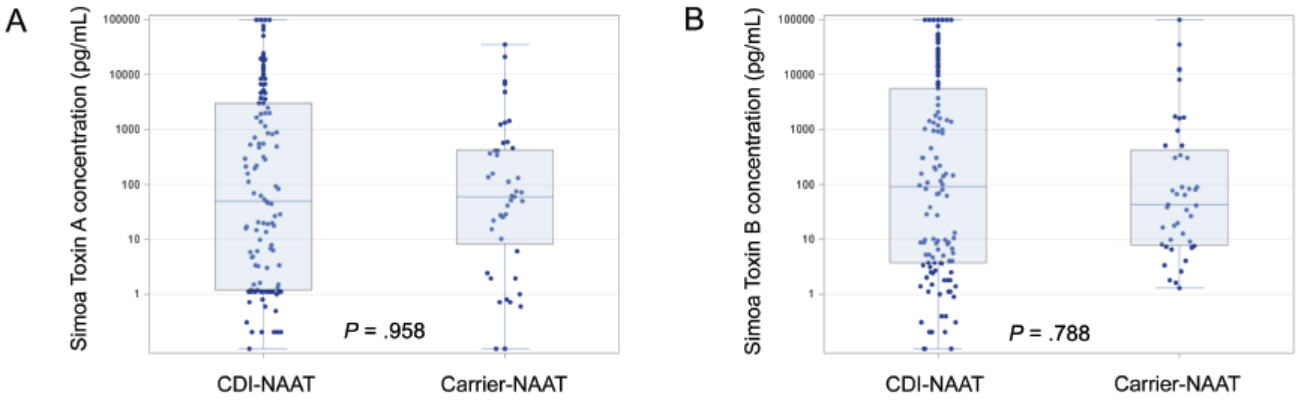
Comparison of *Clostridioides difficile* Stool Toxin Concentrations in Adults With Symptomatic Infection and Asymptomatic Carriage Using an Ultrasensitive Quantitative Immunoassay

Pollock NR, et al. *Clin Infect Dis*. 2019;68:78-86.

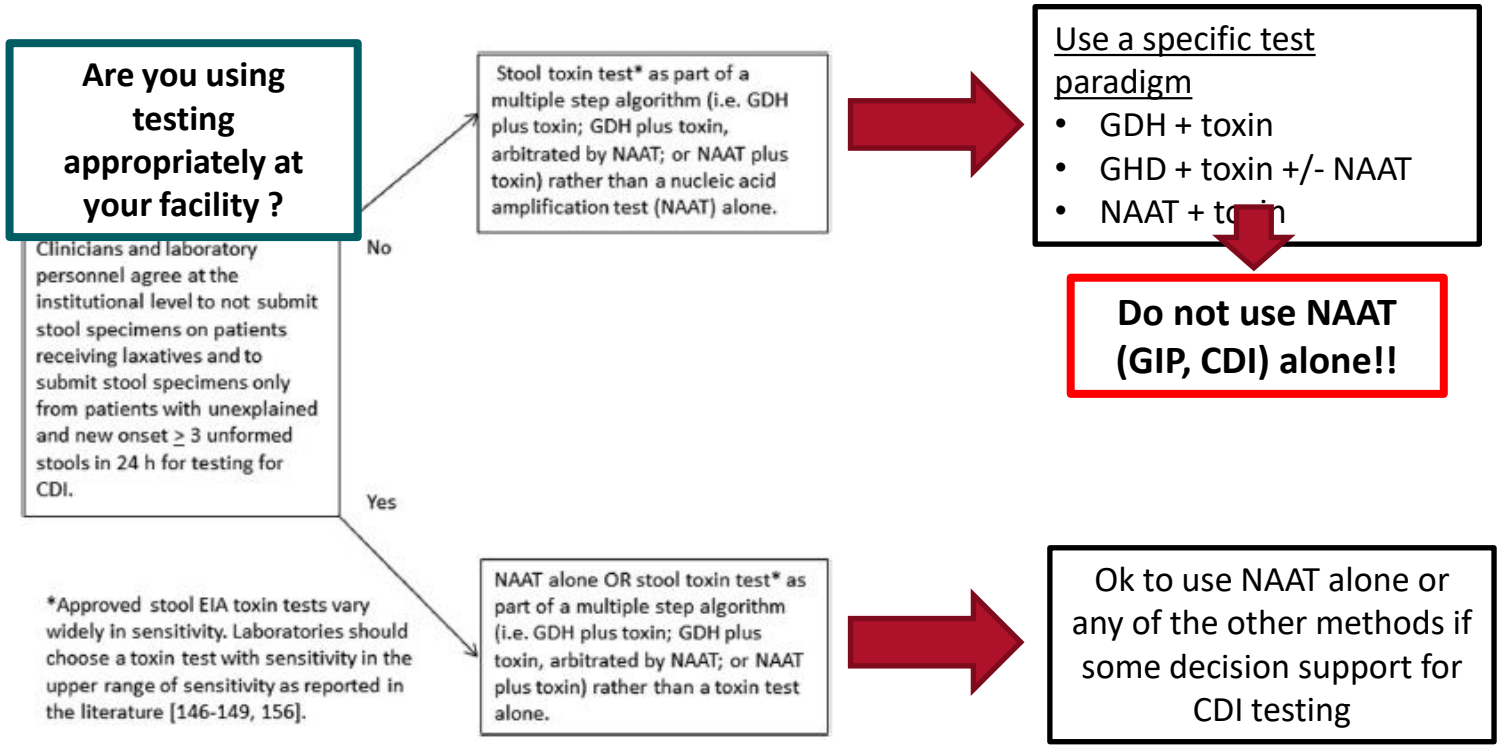
Patients with positive NAAT and diarrhea (N=122) vs. no diarrhea (N=44) had toxin measured using an ultra-sensitive assay

- Toxin levels ranged from 0 to >100,000 pg/ml

Toxin levels did not differentiate symptomatic infections from carriers

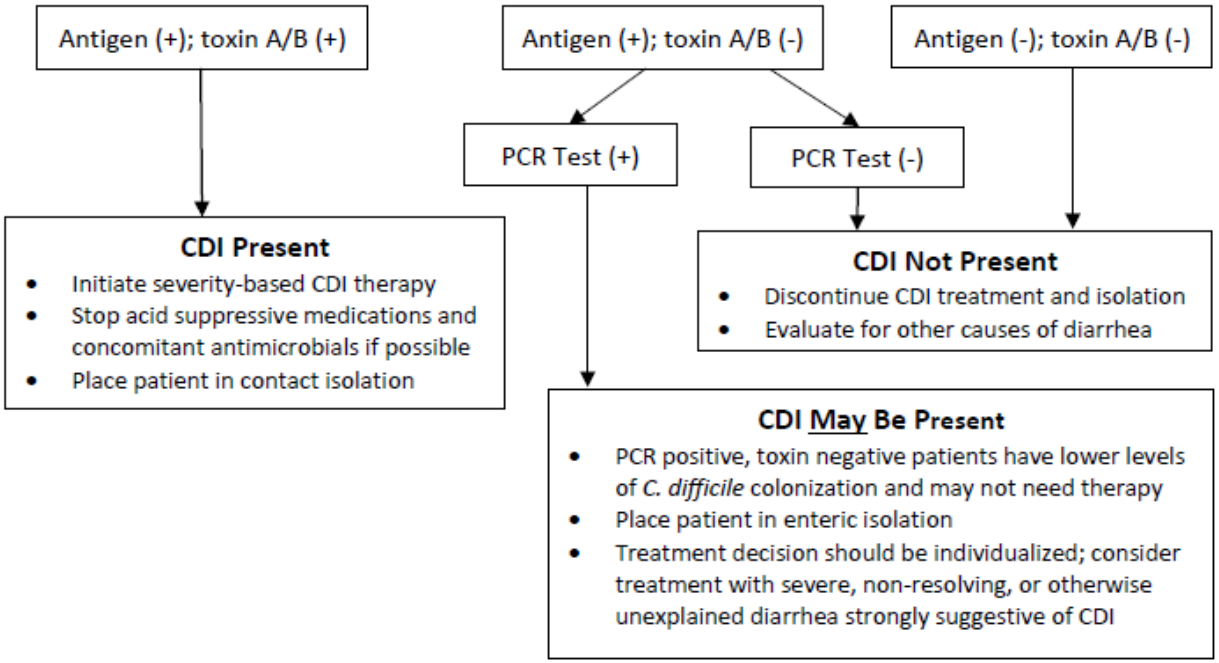


Guideline Recommendations



McDonald LC, et al. *Clin Infect Dis*. 2018;66:e1-48.

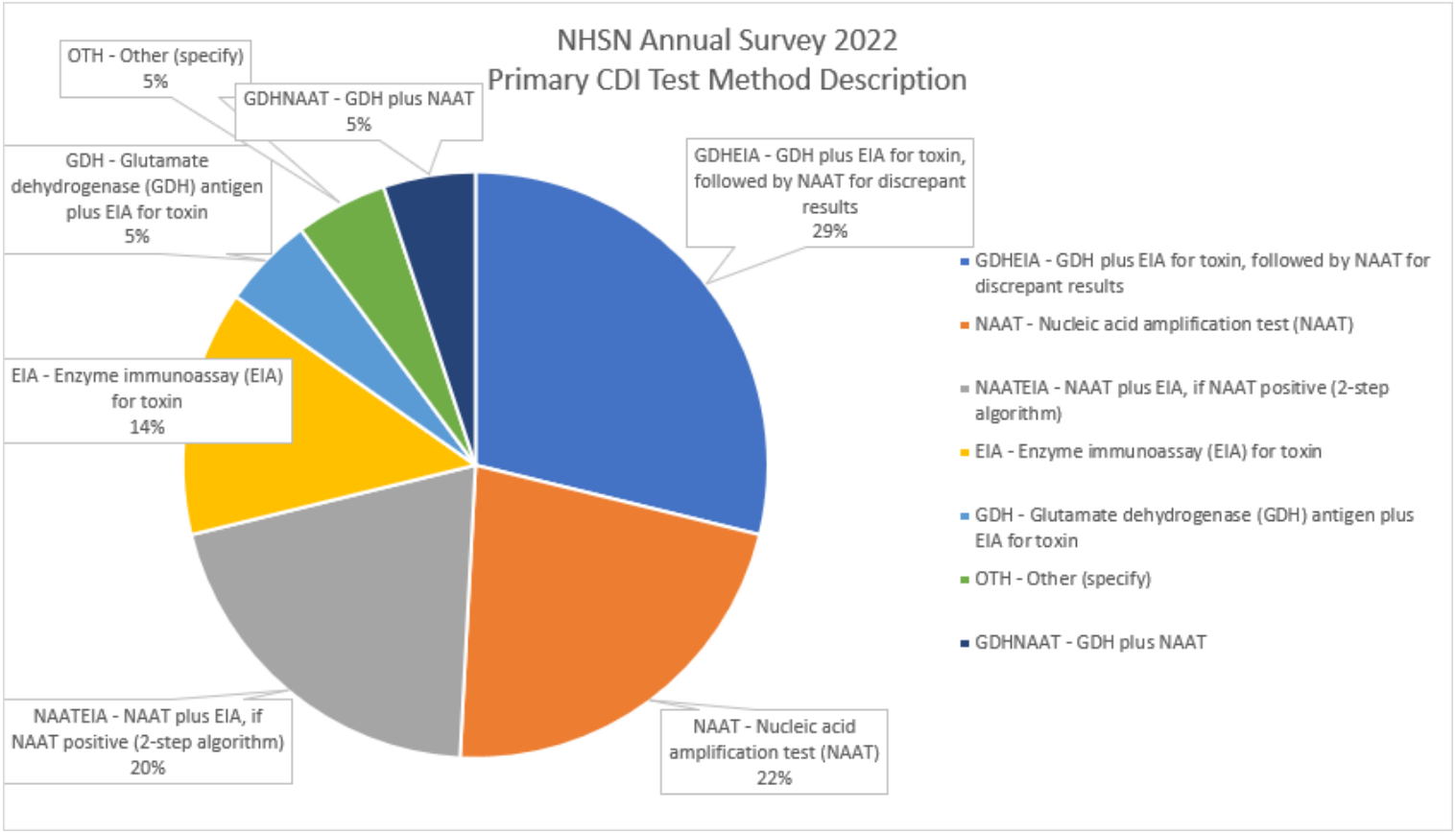
NM CDI Testing Guidelines



www.nebraskamed.com/asp

ASAP

Nebraska De-identified NHSN Data



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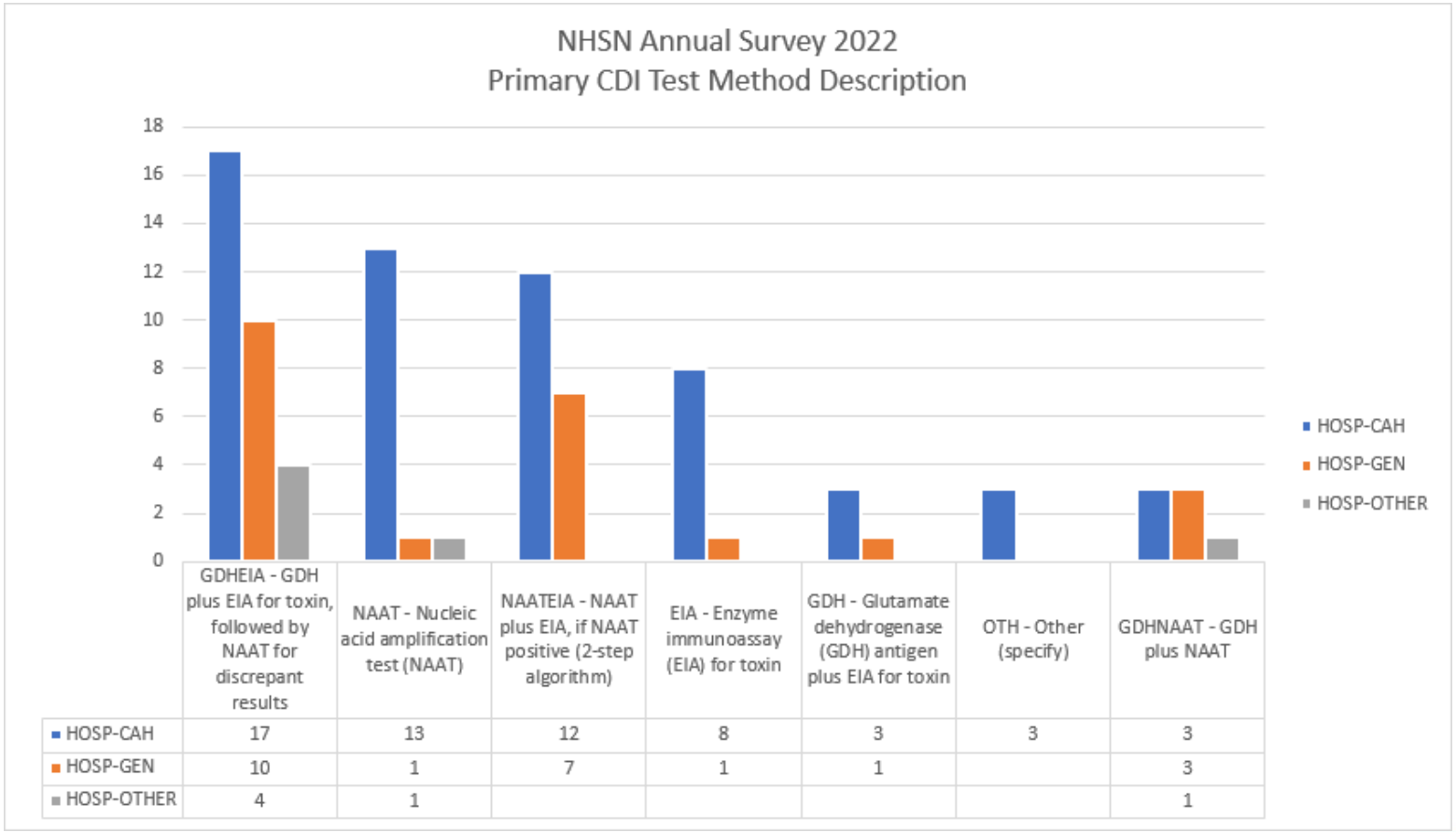
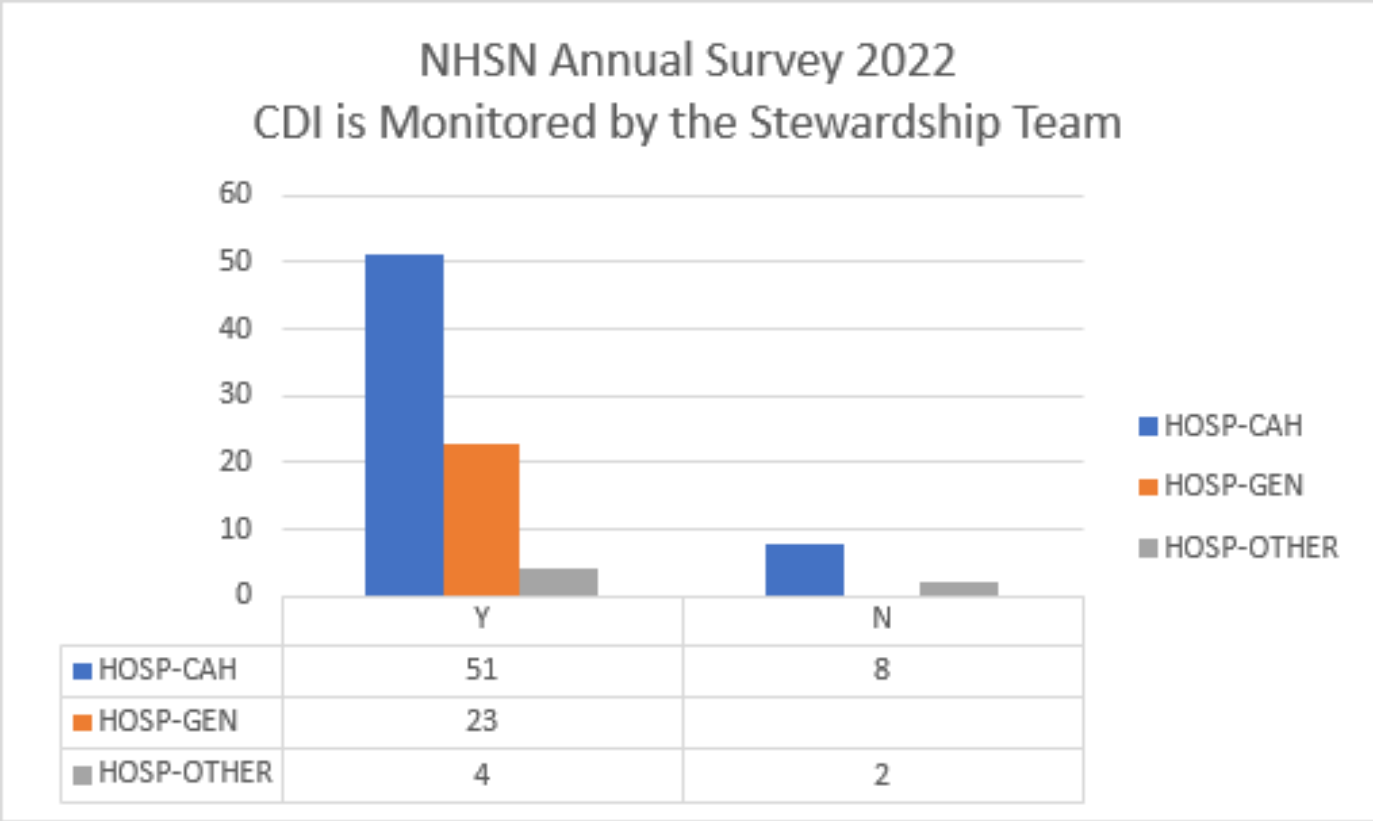


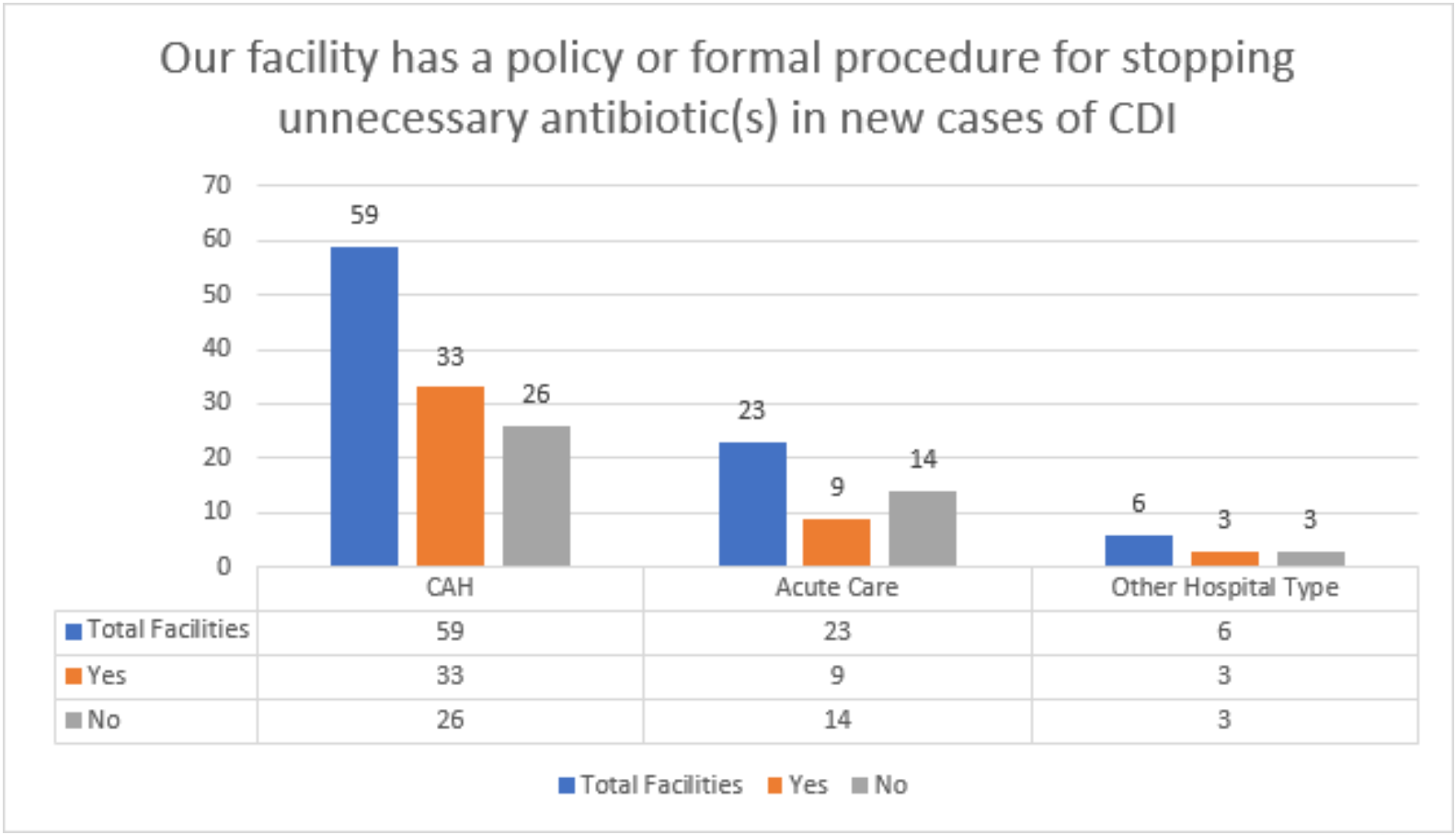
	GDHEIA - GDH plus EIA for toxin, followed by NAAT for discrepant results	NAAT - Nucleic acid amplification test (NAAT)	NAATEIA - NAAT plus EIA, if NAAT positive (2-step algorithm)	EIA - Enzyme immunoassay (EIA) for toxin	GDH - Glutamate dehydrogenase (GDH) antigen plus EIA for toxin	OTH - Other (specify)	GDHNAAT - GDH plus NAAT
HOSP-CAH	17	13	12	8	3	3	3
HOSP-GEN	10	1	7	1	1		3
HOSP-OTHER	4	1					1

Nebraska De-identified NHSN Data



	Y	N
HOSP-CAH	51	8
HOSP-GEN	23	
HOSP-OTHER	4	2

Nebraska De-identified NHSN Data



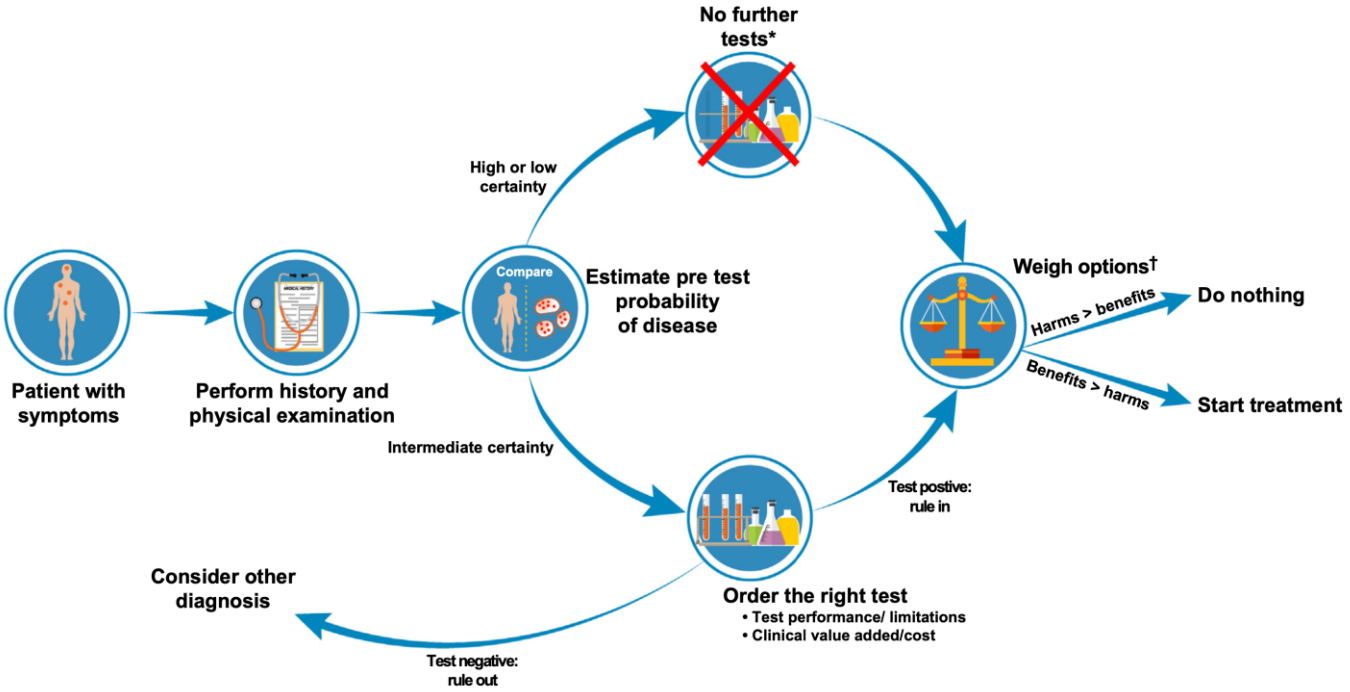
What is diagnostic stewardship and why do we need it?

- Coordinated systems designed to promote evidence-based utilization of diagnostic tests, with the primary goal of improving value and care quality and safely reducing cost.

- Problems with current testing methods:
  - Incorrect interpretation and application to patient's condition
  - Lack of test performance parameter knowledge
  - Lack of prioritization of the clinical examination

Madden et al. Infection Control Hospital Epidemiology. 2018

Ideal testing method



Marjoria et al. The Journal of Molecular Diagnostics. 2020

Computerized Clinical decision support (CCDS)

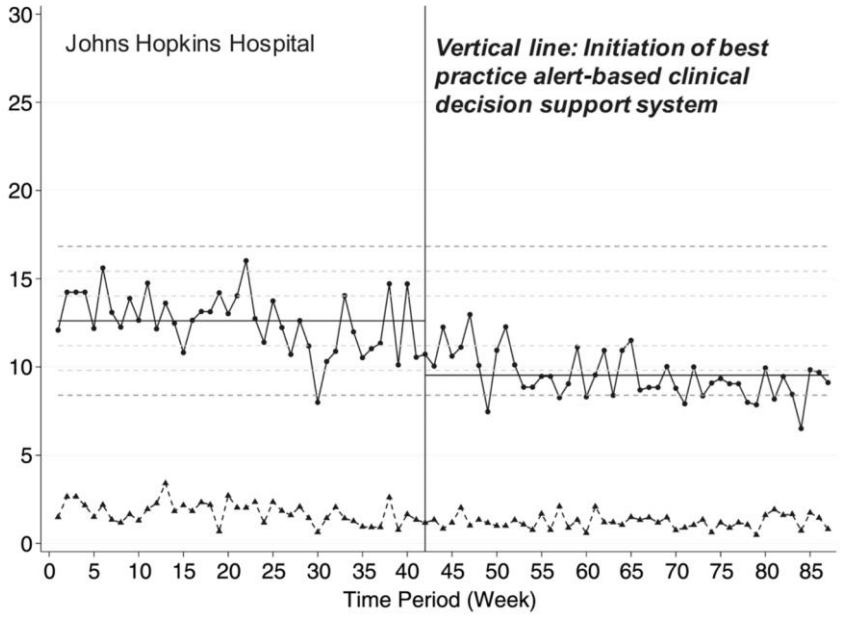
- Any C. difficile order attempt led to a “soft stop” and a hyperlink to C. difficile testing best practices if any of the following conditions were present:
  - Laxative use within the preceding 48h
  - Negative C. difficile test within the previous 7 days
  - Positive test within the previous 14 days.

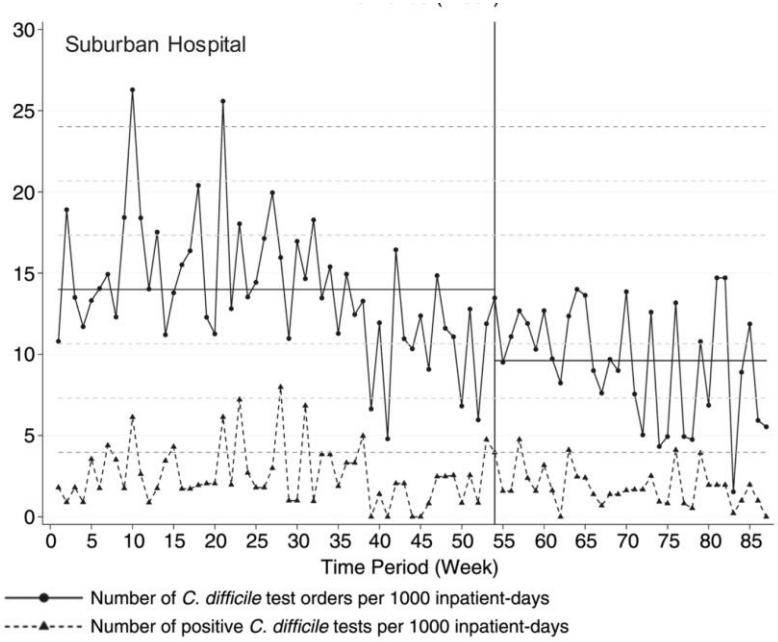
- Providers were instructed to call microbiology if testing was still deemed necessary

- If the provider tried to override the “soft stop”, this led to a second “hard stop” that required a passcode from microbiology to proceed with testing.

Mizusawa et al. Clinical Infectious Diseases. 2019.

Computerized Clinical decision support (CCDS)





12.6 +/- 1.7 → 9.5 +/- 1.3 (**24%**, p <0.001)
Johns Hopkins Hospital

14 +/- 4.2 → 9.6 +/- 3.5 (**31%**, p < 0.001)
Suburban Hospital

Mizusawa et al. Clinical Infectious Diseases. 2019.

Safety Concerns

- Significant adverse effects were defined as CDI-associated death, delayed diagnosis of CDI, or associated ileus or megacolon.

- No predefined adverse events were found in patients managed with CCDS

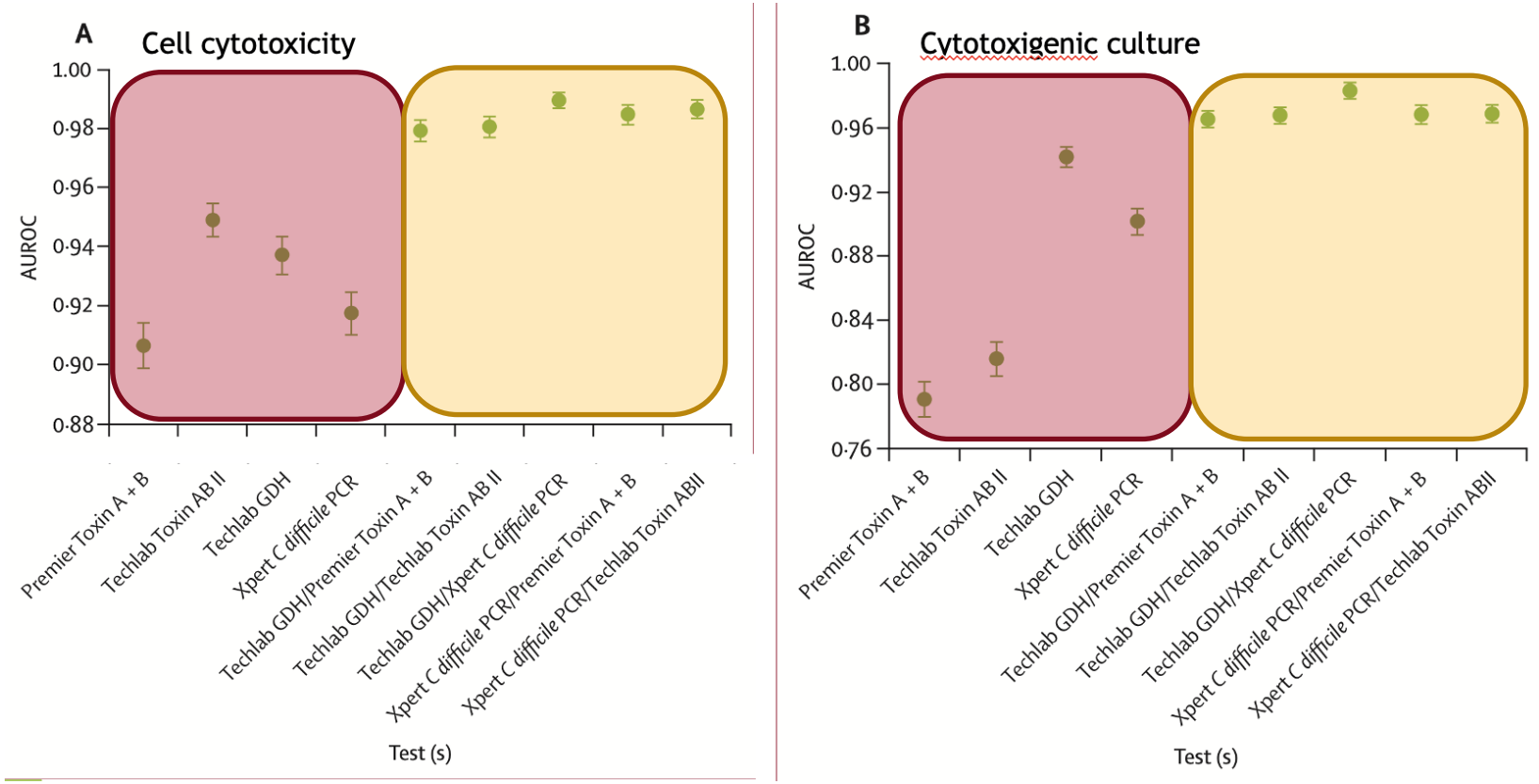
Mizusawa et al. Clinical Infectious Diseases. 2019.

Multistage Algorithm

- No ideal standalone method exists for the diagnosis of C. difficile infection.

- Multistage algorithms have shown better performance and are now recommended by the Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

Commercial Testing VS Reference Methods

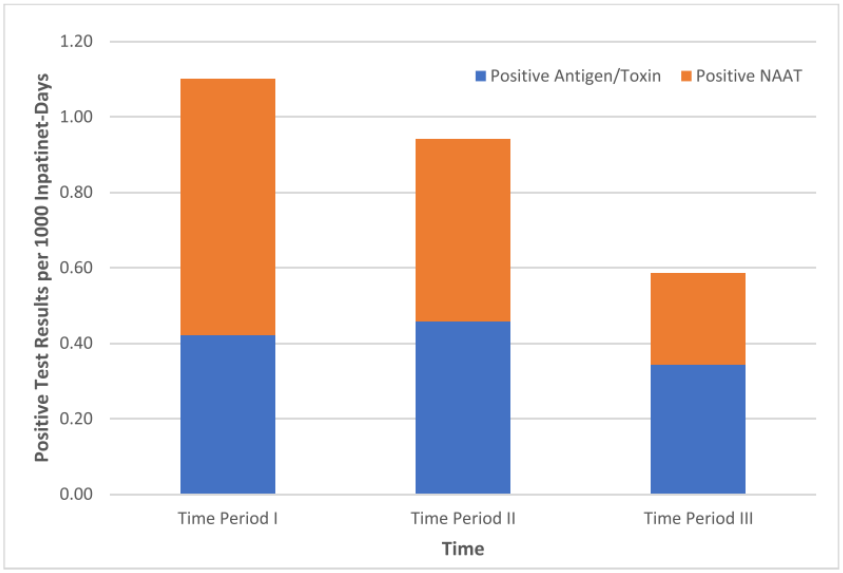


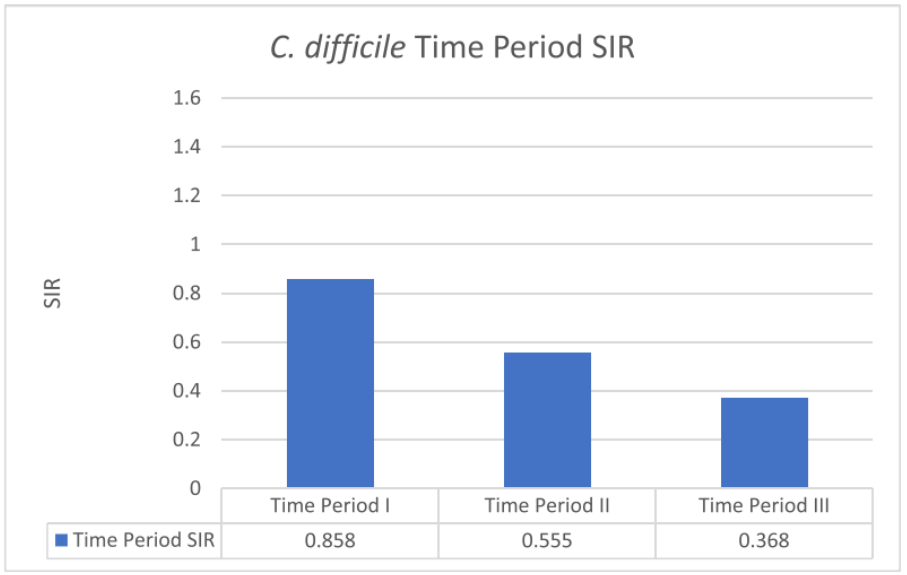
Single-step testing

Two-step testing

Planche et al. The Lancet Infectious Diseases. 2013

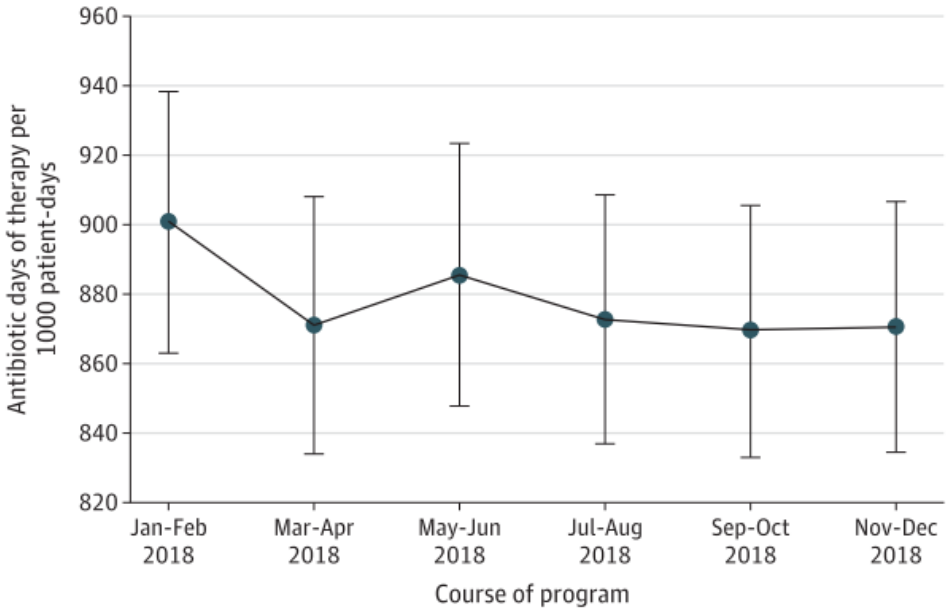
Eliminating Reflex Testing





Khuvis et al. Clinical Biochemistry. 2023

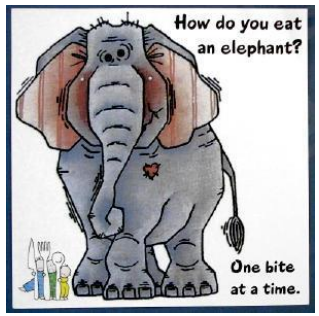
Don’t Forget about Antimicrobial stewardship AHRQ Safety program

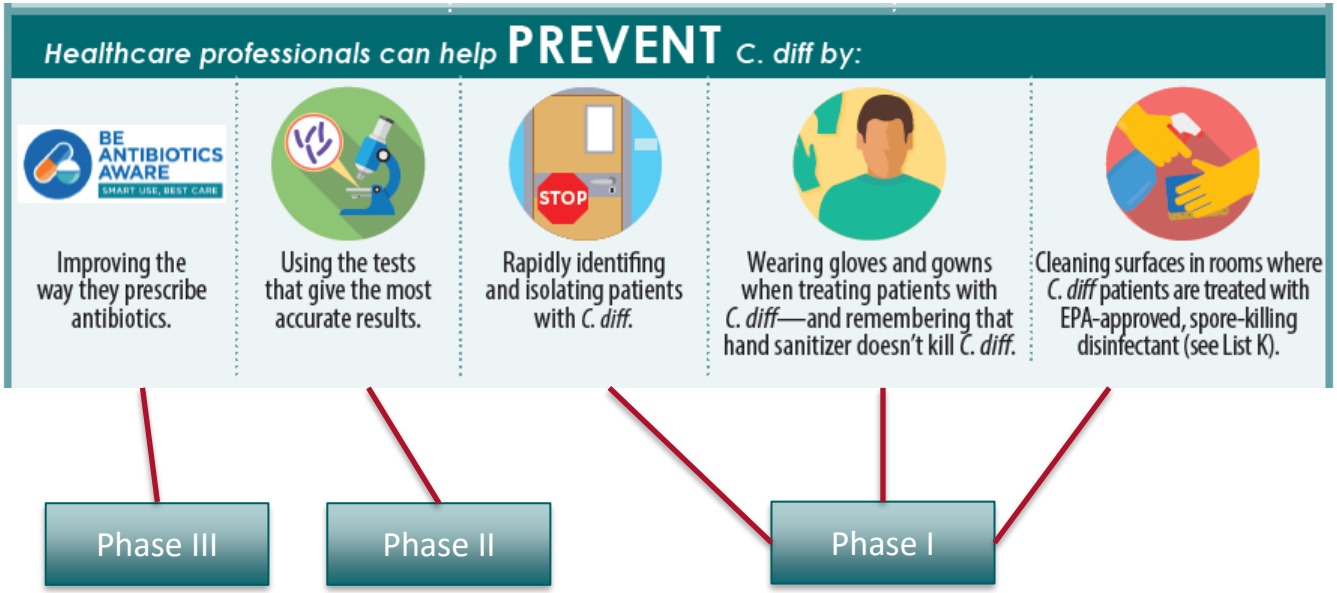


- The incidence rate of hospital-onset C difficile LabID events decreased from quarter 1 to quarter 4
- 19.5% (95% CI, −33.5% to −2.4%, P = .03)

Tamma et al. JAMA Network Open. 2021

Tackling HO - CDI…





Addressing Appropriate Testing Practices

- Implemented stricter specimen rejection policy
  - Stick test
- Cessation of provider notification regarding cancelled tests

LAB ALERT

Date: August 24, 2018

To: Nebraska Medicine Physicians & Staff and UNMC Medical Staff and House Officers, UNMCP Outpatient Clinics and Regional Pathology Services Clients

From: Paul D. Fey, Ph.D., Amy Crismon, MT (ASCP) SM, Nebraska Medicine Microbiology

RE: Change in *C. difficile* rejection policy

As part of a joint undertaking with Infection Control and a committee working toward a reduction of *C. difficile* infections at Nebraska Medicine, several institution wide changes are being implemented. One such change will be the institution of a stricter policy for the rejection of formed and semi-formed stool for *C. difficile* testing by the Clinical Microbiology laboratory. Effective Monday, August 27th, we will cease calling providers regarding cancelled *C. difficile* tests and will attach the following comment to the credited test:

> Stool submitted not acceptable for testing. Test credited. Only loose or watery stool is appropriate for *C. difficile* testing. If testing clinically indicated or if an ileus is suspected, please consult the Microbiology Director.

NM Guideline Recommendations

Manage diarrhea assuming CDI is unlikely to be the cause

- 50% of people who tested + for CDI had received cathartic agent within previous 24 hours

Reserve CDI testing to following populations

- Significant diarrhea (>3 BMs in <24 hours) and at least one CDI Sx:
  - Unexplained elevation in WBC count or fever (isolated leukocytosis without diarrhea is not an indication for CDI testing)
  - New onset abdominal pain and/or distention with diarrhea
- Severe diarrhea (>7 bowel movements or >1.5L over 24 hours)
- Persistent diarrhea = significant diarrhea for >24 hours which is not resolved with conservative treatment and does not have another explanation

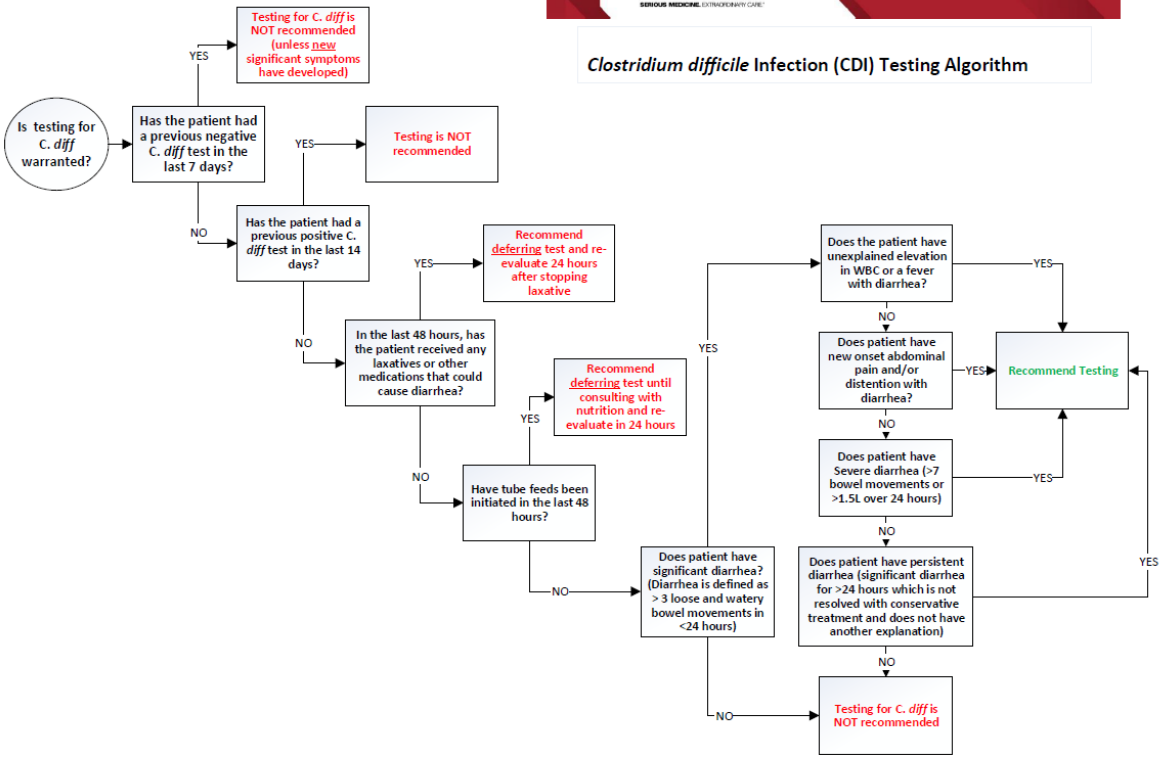
Do Not Test: asymptomatic, infants (<1 year), formed stool, or “test for cure”

Do not repeat test within at least 7 days

Addressing Appropriate Testing Practices

Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

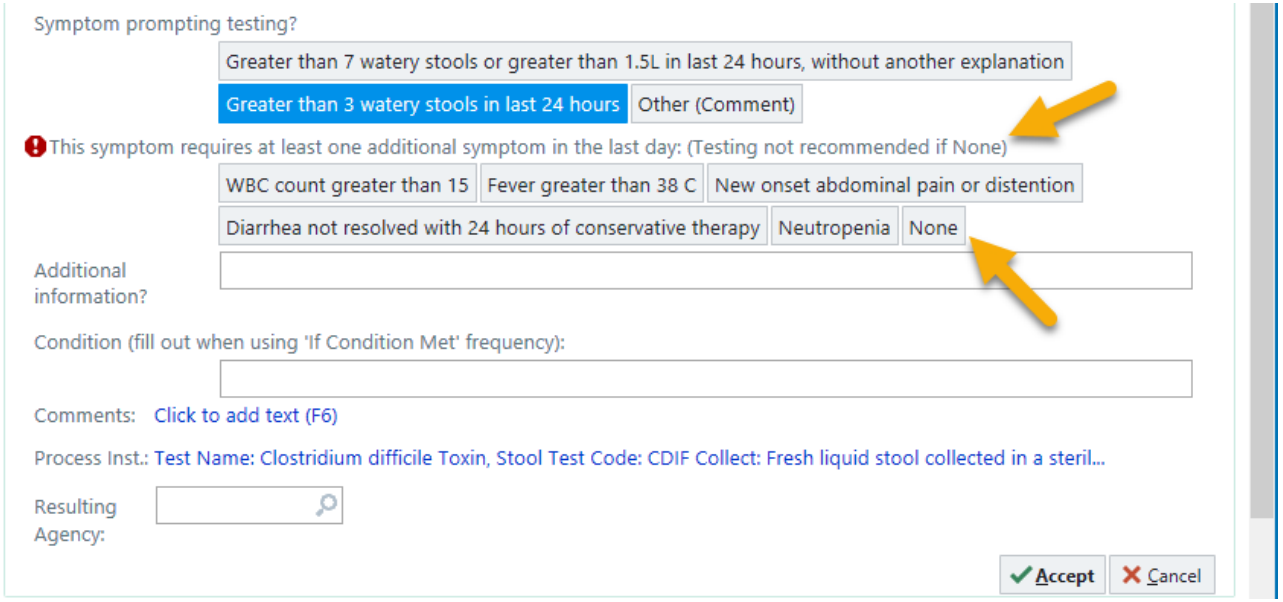
Clostridium difficile Infection (CDI) Testing Algorithm



ASAP

Addressing Appropriate Testing Practices

Implemented new order to ensure appropriate testing



Addressing Appropriate Testing Practices

A refreshable report was developed and visible when ordering C diff testing

- Goal of providing pertinent information when ordering test

DUPLICATE TEST - TESTING NOT RECOMMENDED

This is repeat test within 7 days of a negative test.

C. diff Tox
Date
09/11/2018
09/11/2018
09/11/2018
09/11/2018
C difficile
Date
09/11/2018

TESTING CONTRAINDICATED!

The Clostridium Difficile order CANNOT be signed because a "drug

Stool Documentation

Patient must have greater than 7 watery stools or greater in the last 24 hours another explanation OR patient must have greater than 3 water stools in the plus additional symptoms.

Stool Documentation (last day)

Date/Time	Stool Appearance	Stool	Stool Occurrence	Stool Amount	Stool Source
09/11/18 2005	Formed	--	--	Small	Rectum
09/11/18 1945	--	--	1	--	--
09/11/18 1526	--	--	1	--	--
09/11/18 0800	--	--	1	--	--

Tube Feed Orders

Patient has active tube feed orders. If new tube feeds have been initiated in the last 48 hours, defer test until consulting with nutrition and re-evaluate in 24 hours.

Tube Feed
Start
09/11/18 1626

Temperature (min/max in last 24 hours)

Temp Min: 37.1 °C Max: 37.4 °C

White Blood Cell Count (most recent 3 in last 72 hours)

WBC (X10E3/uL)
Date/Time Value
10/16/2018
10/15/2018

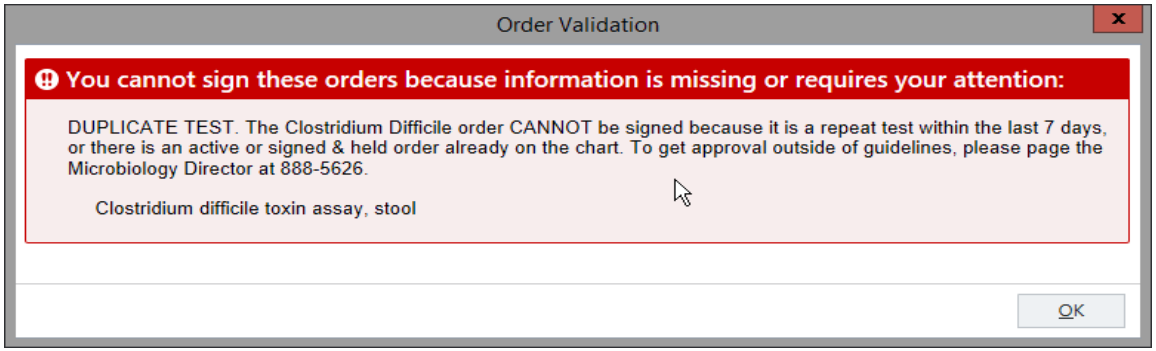
Patient-specific C.diff Risk Factors

- Active high CDI risk antibiotic
- Active PPI order
- Age 65 and up
- Immunosuppression

Addressing Appropriate Testing Practices

Hardstop validation tool to decrease duplicate testing and testing when laxative has been recently given

- No repeat within 7 days
- No testing within 24 hours of laxative agent being administered



! TESTING CONTRAINDICATED!

The Clostridium Difficile order **CANNOT be signed** because a "drug for constipation" has been administered in the last 24 hours.

- **Discontinue** "drug(s) for constipation" & Re-evaluate need for test 24 hours after discontinuing medication(s).
- To get approval outside of guidelines, please page the Microbiology Director at 402-888-5626.

Administrations in Last 24 hours:	**Active Drug(s) for Constipation:**
docusate sodium 10/28/2020 9:35 PM, 10/29/2020 9:12 AM	docusate sodium

Lab Results (last 720 hours/30 days)

Clostridium Difficile Toxin Assay
No results found for: CDIFAB

Clostridium Difficile DNA
No results found for: CDIFD

Stool Documentation

Patient must have greater than 7 watery stools or greater in the last 24 hours, without another explanation OR patient must have greater than 3 watery stools in the last 24 hours plus additional symptoms.

Stool Documentation (last day)

Date/Time	Stool Appearance	Stool	Stool Occurrence	Stool Amount	Stool Source
10/28/20 1600	—	—	—	—	Rectum
10/28/20 1200	—	—	—	—	Rectum
10/28/20 0921	Brown	—	1	Large	Rectum
10/28/20 0757	—	—	—	—	Rectum
10/28/20 0745	—	—	—	—	Rectum
10/28/20 0036	Brown	—	1	Small	Rectum

Enteric Contact isolation is recommended for patients with suspected Clostridium difficile. Please use Enteric Contact isolation in addition to any other isolation the patient is currently in. See patient header to determine patient's current isolation status.

NM Cost (not price to patient): $61, if reflexed to DNA test

Clostridium Difficile testing **NOT RECOMMENDED** if:

- Formed stool
- Non clinically significant diarrhea
- Tube feeds initiated in last 48 hours
- Drug(s) for constipation administered in last 24 hours
- Duplicate test in 7 days
- Duplicate positive test in 14 days

Clostridium difficile testing algorithm

Clostridium difficile toxin assay, stool ($19) — Accept | Cancel

P

Frequency: Once | Tomorrow AM | Daily AM (default 3 days) | STAT | Once | Once timed | Add-On

Starting: 10/29/2020 | Today | Tomorrow | At: 1355

First Occurrence: **Today 1355**

Scheduled Times

10/29/20 1355

Specimen Src: Stool

Symptom prompting testing? Greater than 7 watery stools or greater than 1.5L in last 24 hours, without another explan ... | Greater than 3 watery stools in last 24 hours | Other (comment)

This symptom requires at least one additional symptom in the last day:

- ☐ WBC count greater than 15
- ☐ Fever greater than 38 C
- ☐ New onset abdominal pain or distention
- ☐ Diarrhea not resolved with 24 hours of conservative therapy
- ☐ Neutropenia
- ☐ Other (comment)

Additional information?

Addressing Appropriate Testing Practices

Improve nursing stool documentation

- Created a standardized tool for nursing stool assessment

The "Stool Tool"

Stool Amount

Select Single Option: (F5)

- Large
- Medium
- Small
- Smear
- UTA=Unable to assess
- Other (Comment)

Comment (F6)

Stool Appearance

Select Multiple Options: (F5)

- Mucus
- Red
- Green
- Grey
- White
- Brown
- Tan
- Black
- Yellow
- Other (Comment)

Comment (F6)

Stool Type

Select Single Option: (F5)

- Formed
- Loose
- Liquid

Comment (F6)

Row Information

Nebraska Medicine Stool Assessment Tool (NSAT)

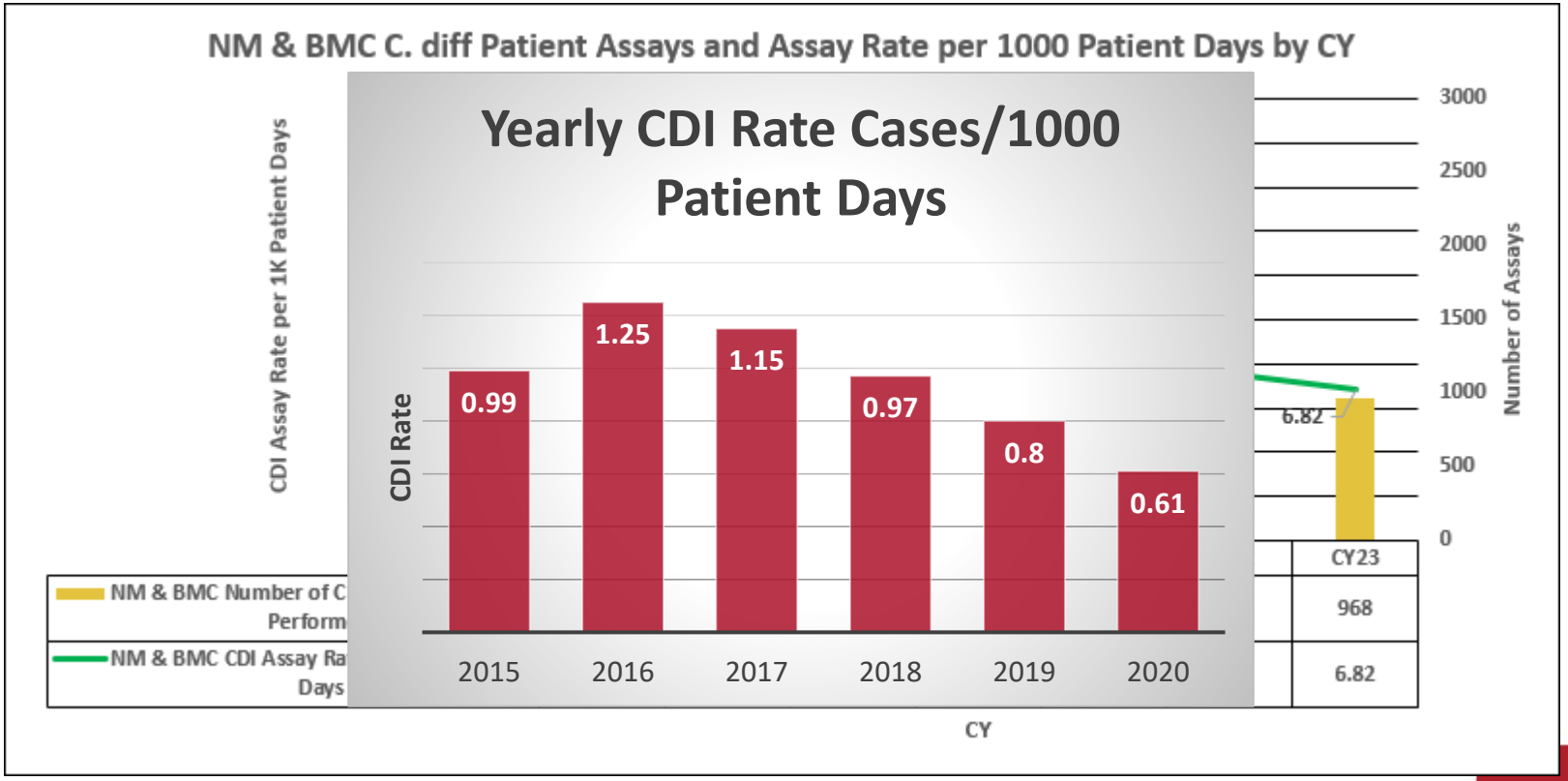
FORMED (hard and soft)	Hard, individual lumps, balls	
	Formed like a sausage with attached lumps	
	Sausage or log shaped, may have cracks or be smooth	
LOOSE	Soft small balls with clear edges – not well defined	
	Fluffy and mushy	
LIQUID	Liquid with no solid pieces	

ASAP

CDI Testing Rate and CDI Case Rate

CDI Testing Rate

- 2017-18: 12.5/1000 PD
- 2019-6/2020: 7.8/1000 PD



Conclusions

- Numerous strategies exist for CDI testing
- NAAT testing alone is not an ideal strategy
- Support for appropriate test ordering improves test utilization and safely decreases CDI rates (if done correctly)