Clostridium difficile Infection (CDI) Guideline Update:

Understanding the Data Behind the Recommendations

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A Webinar for HealthTrust Members

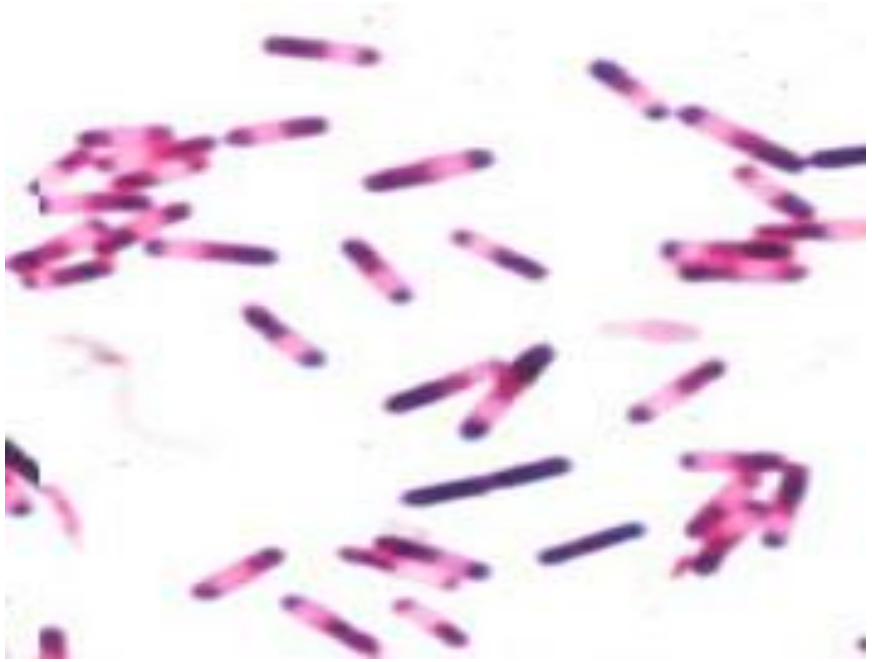
September 24, 2018

Summary of Key Changes from 2010 Guidelines

- Epidemiology
  - 027/NAP1/BI strain possibly on the mend
- Diagnosis
  - Still not completely satisfying
- Infection prevention and control
  - Nothing really new
  - Too early to know what to do with asymptomatic carriers
- Treatment
  - Major changes
  - Should result in improved outcomes

Clostridium difficile

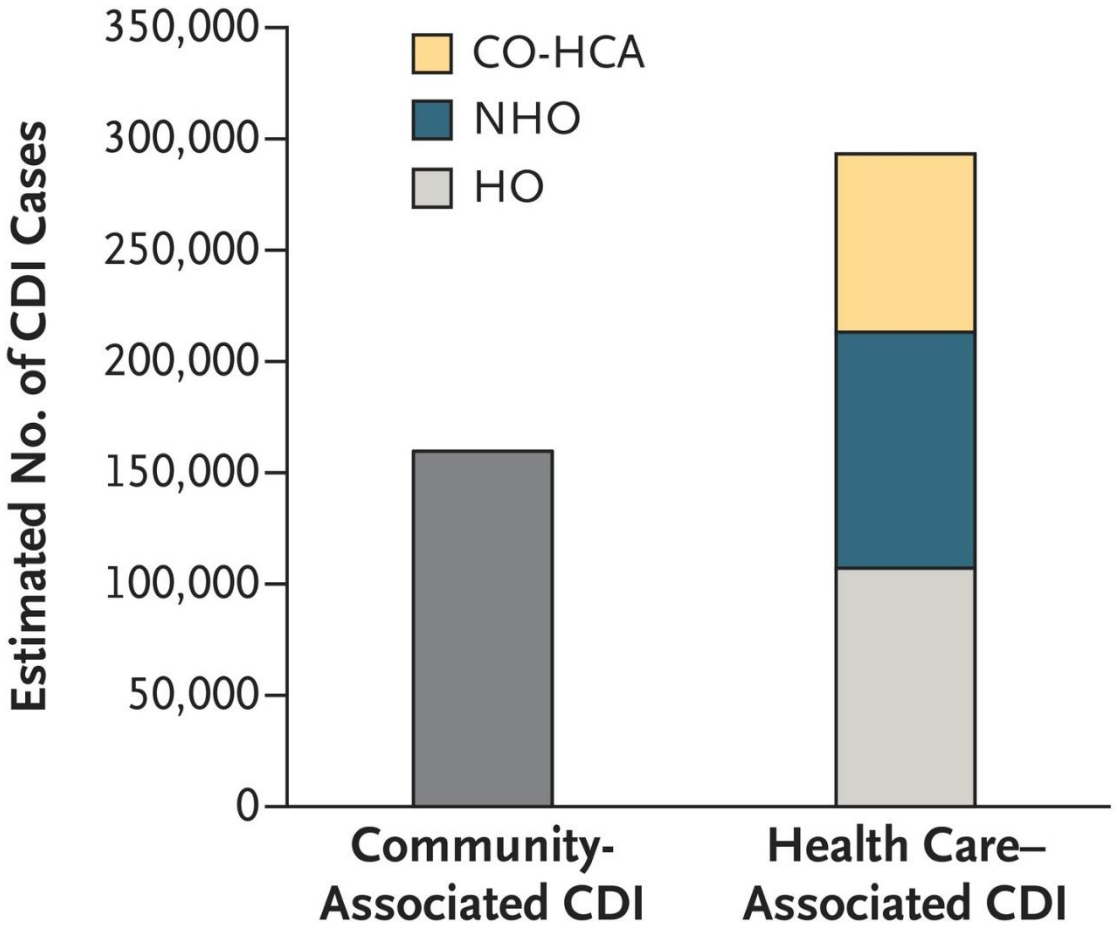
- Gram positive, spore forming rod
- Obligate anaerobe
- Toxin A and Toxin B
  - Required to cause disease (toxigenic)
    - 20% to 30% non-toxigenic
  - *C. difficile* infection (CDI, formerly CDAD)
    - Toxigenic *C. difficile* in stool ≠ CDI



- Ubiquitous organism: soil, water, pets, livestock, food, homes of otherwise healthy people, healthy people

CDI Epidemiology

- Best surveillance in US: CDC Emerging Infections Program
- Seminal paper on CDI published in 2015
  - Data from 2011
- Key findings
  - 147 incident CDI cases / 100,000 persons
    - >450,000 incident cases
    - >29,000 associated deaths
  - More community-onset cases than previously recognized
  - 027 strain: 31% healthcare-associated CDI, 19% community-associated CDI



Lessa. NEJM. 2015

Declines in 027 since 2011

	2011	2012	2013	2014	2015
Incidence (per 100,000)	147.2	145.8	141.8	141.7	148.6
027: Healthcare associated (%)	31%	21%	24%	14%	19%
027: Community associated (%)	19%	17%	12%	7%*	8%*

*not most common strain

https://www.cdc.gov/hai/eip/clostridium-difficile.html

Diagnostics Available

Test	Advantage(s)	Disadvantage(s)
Toxin testing		
Toxin Enzyme immunoassay (EIA)	Rapid, simple, inexpensive	Least sensitive method, assay variability
Tissue culture cytotoxicity	More sensitive than toxin EIA, associated with outcomes	Labor intensive; requires 24–48 hours for a final result, special equipment;
Organism identification		
Glutamate dehydrogenase (GDH) EIA	Rapid, sensitive	Non-toxigenic and toxigenic *C. difficile* detected;
Nucleic acid amplification tests (NAAT) (PCR)	Rapid, sensitive, detects presence of toxin gene	Cost, special equipment, may be “too” sensitive
Stool culture	Most sensitive test available when performed appropriately	Non-toxigenic and toxigenic *C. difficile* detected; labor-intensive; requires 48–96 hours for results

Historical Flaws in Diagnostic Literature Interpretation

- Lack of clinical data
  - Test for CDI does not exist: detect toxin or organism
    - Up to 15% of patients admitted to the hospital are colonized with toxigenic *C. difficile*
    - Other reasons for diarrhea are often present
  - Enhanced sensitivity for *C. difficile* detection will increase detection of asymptomatic *C. difficile* carriage
    - Patients with CDI have more toxin / organism in stool than asymptomatic carriers

- Lack of appreciation not all toxin detection assays are equal
  - Original EIAs: detect toxin A only
    - Some strains produce only toxin B (as many as 20%)
  - Manufacturer, target(s) and format make a difference

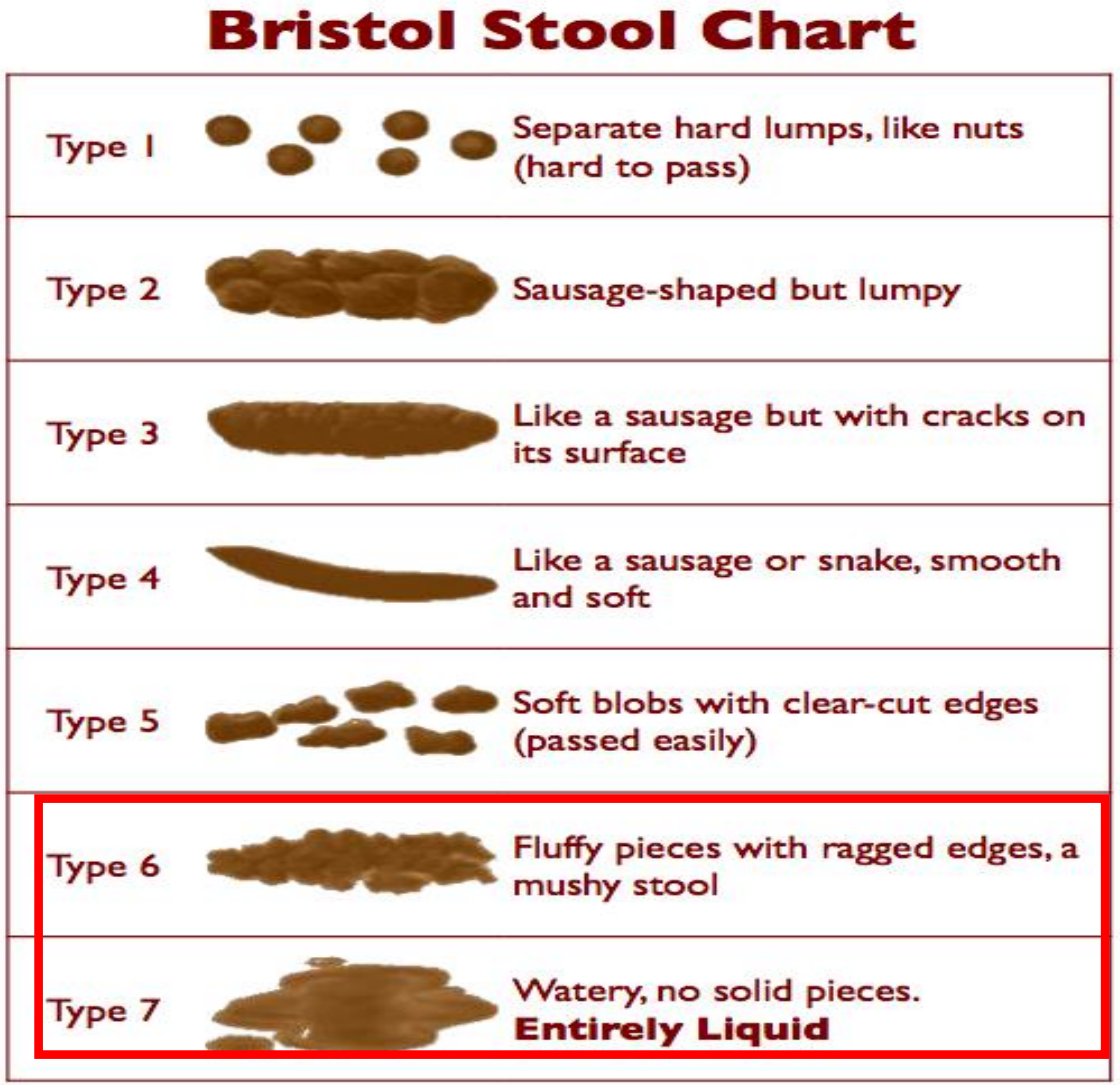
Dubberke. AAC. 2015; Peterson, CID. 2007

Types of False Positive Tests for CDI

- Toxigenic *C. difficile* present but no CDI
  - Concern of more sensitive tests
    - GDH
    - NAAT/PCR
    - Culture
- Assay result positive but toxigenic *C. difficile* not present
  - Tests that detect non-toxigenic *C. difficile*
    - GDH alone
    - Culture alone
  - False positive test

Enhanced Sensitivity to Detect *C. difficile* Decreases Specificity for CDI

- Including clinically significant diarrhea in gold standard:
  - No impact on sensitivity
    - NAATs 99%
    - Techlab Tox AB II 94%
  - Specificity of NAATs decreased from ~98% to ~89% ($p < 0.01$)
    - Positive predictive value decreased to **~60%** (25% drop)
  - No NAAT (+) / toxin (–) developed CDI-related complications



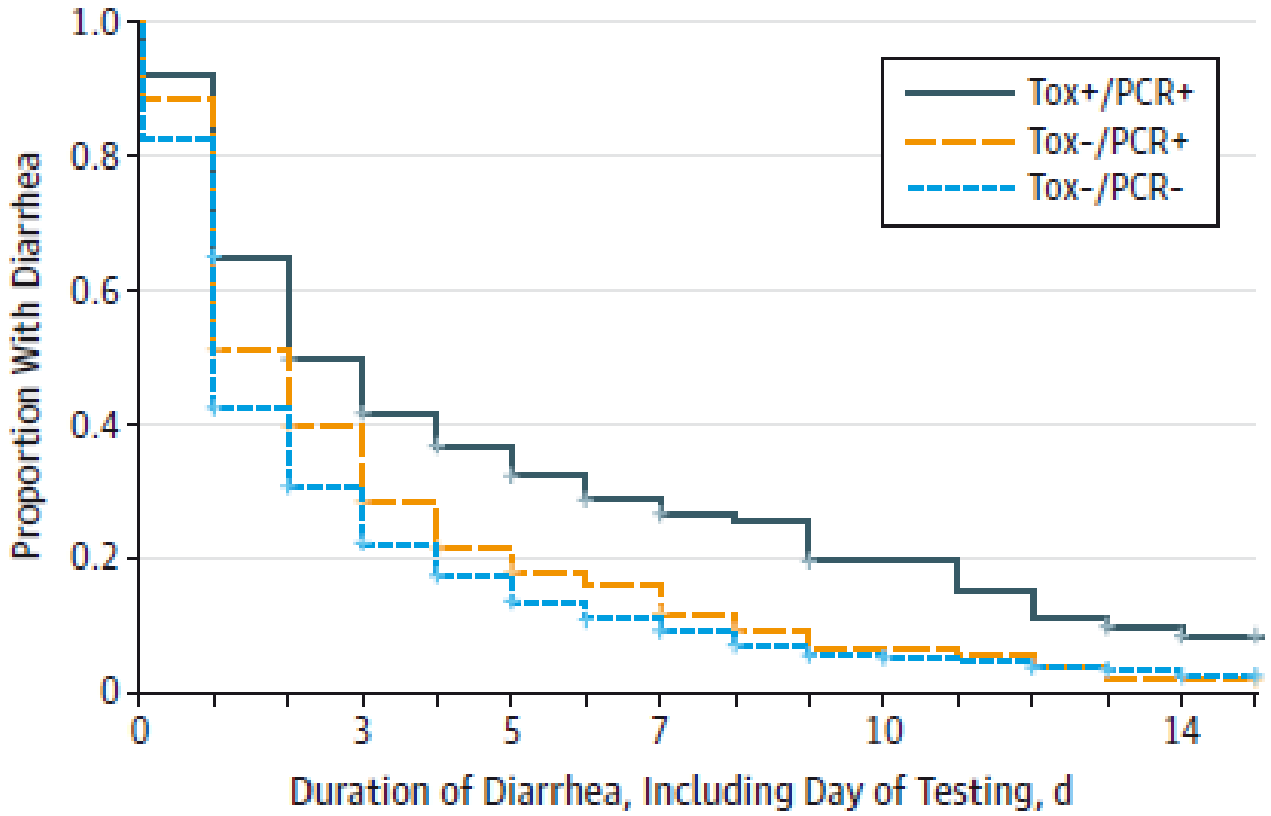
Dubberke. JCM. 2011;

Largest Assay Comparison To Date

Variable	Cytotoxicity (CTX) +	CTX -/ NAAT +	-/-	(CTX+) vs. (CTX-/NAAT+)	(CTX+) vs. (-/-)	(CTX-/NAAT+) vs. (-/-)
Number	435	311	3943			
White blood count (SD)	12.4 (8.9)	9.9 (6.6)	10.0 (12.0)	<0.001	<0.001	0.863
Died	72 (16.6%)	30 (9.7%)	349 (8.9%)	0.004	<0.001	0.606

Planche. Lancet ID. 2013

Time to Resolution of Diarrhea



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

Polage. JAMA IM. 2015

Guidelines: Diagnosis

Clinical question: What is the preferred population for *C. difficile* testing, and should efforts be made to achieve this target?

- Patients with unexplained and new-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI (weak recommendation, very low quality of evidence)

Limitations Noted

- Weak supportive data on definition for clinically significant diarrhea
  - Has changed over time
  - Other conditions / medications can confound
- Suggest ways to improve patient selection:
  - Clinicians: order tests only on patients likely to have CDI
  - Laboratories: reject specimens that are not soft/liquid (i.e. take the shape of the container)

Author	Year	Definition
Tedesco	1974	> 5 loose BM/day
Teasley	1983	> 6 loose BM over 36 hours
Fekety	1989	Liquid OR >4 BM per day for ≥3 days
Johnson	2013	≥3 loose or watery BM in 24 hours

McDonald. CID. 2018

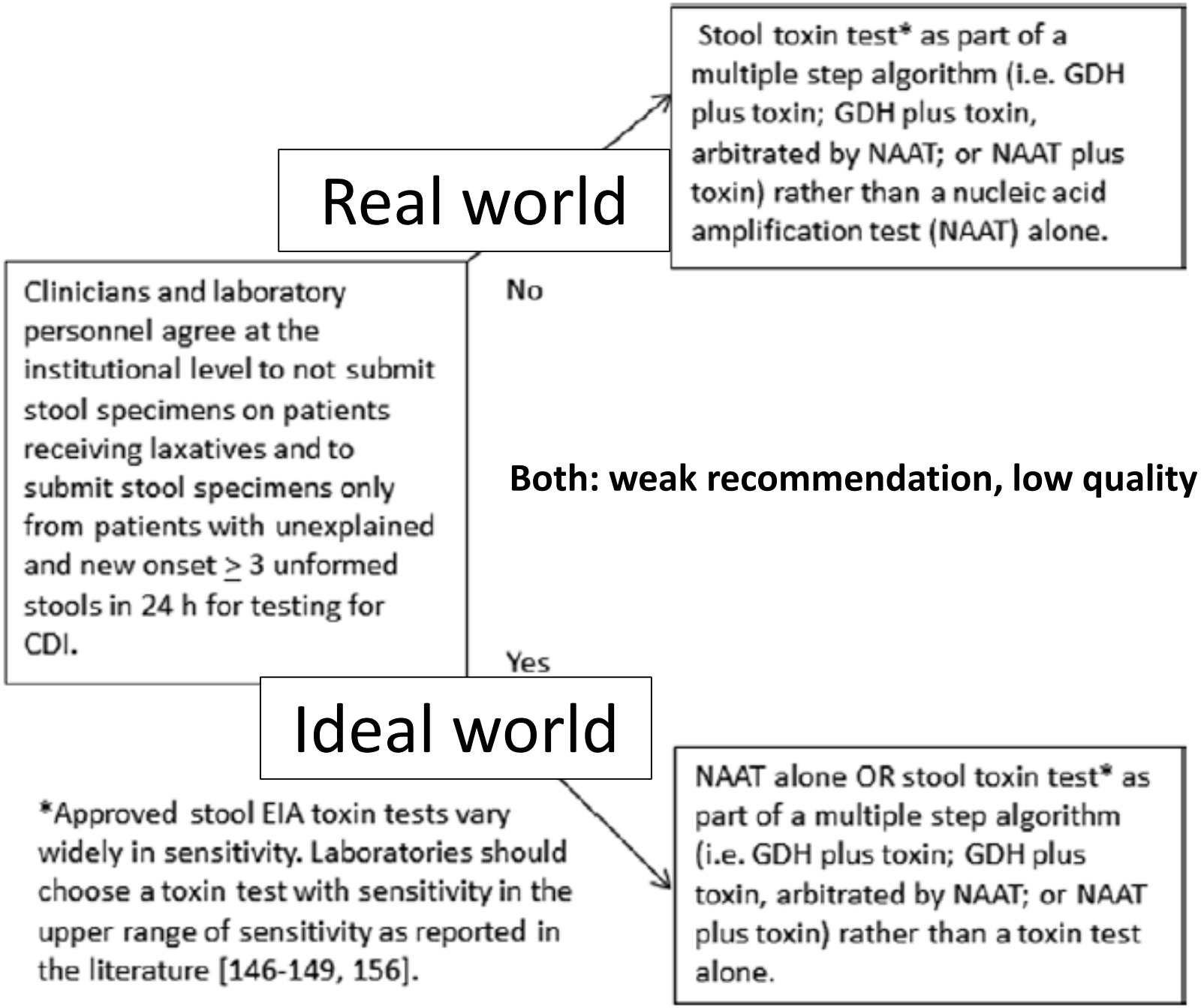
Supportive Evidence for Clinicians

			=5)
Positive toxin			
Positive toxig			
Negative EIA treatment			
Negative EIA and CDI diagnosed in next 30 days	0	0	0
90-day mortality	0	1	0

Take home messages:

- If clinical judgement used: 65% did not need to be tested
- If we used NAAT, 9 “CDI cases” vs. 4

Kwon. JCM. 2017



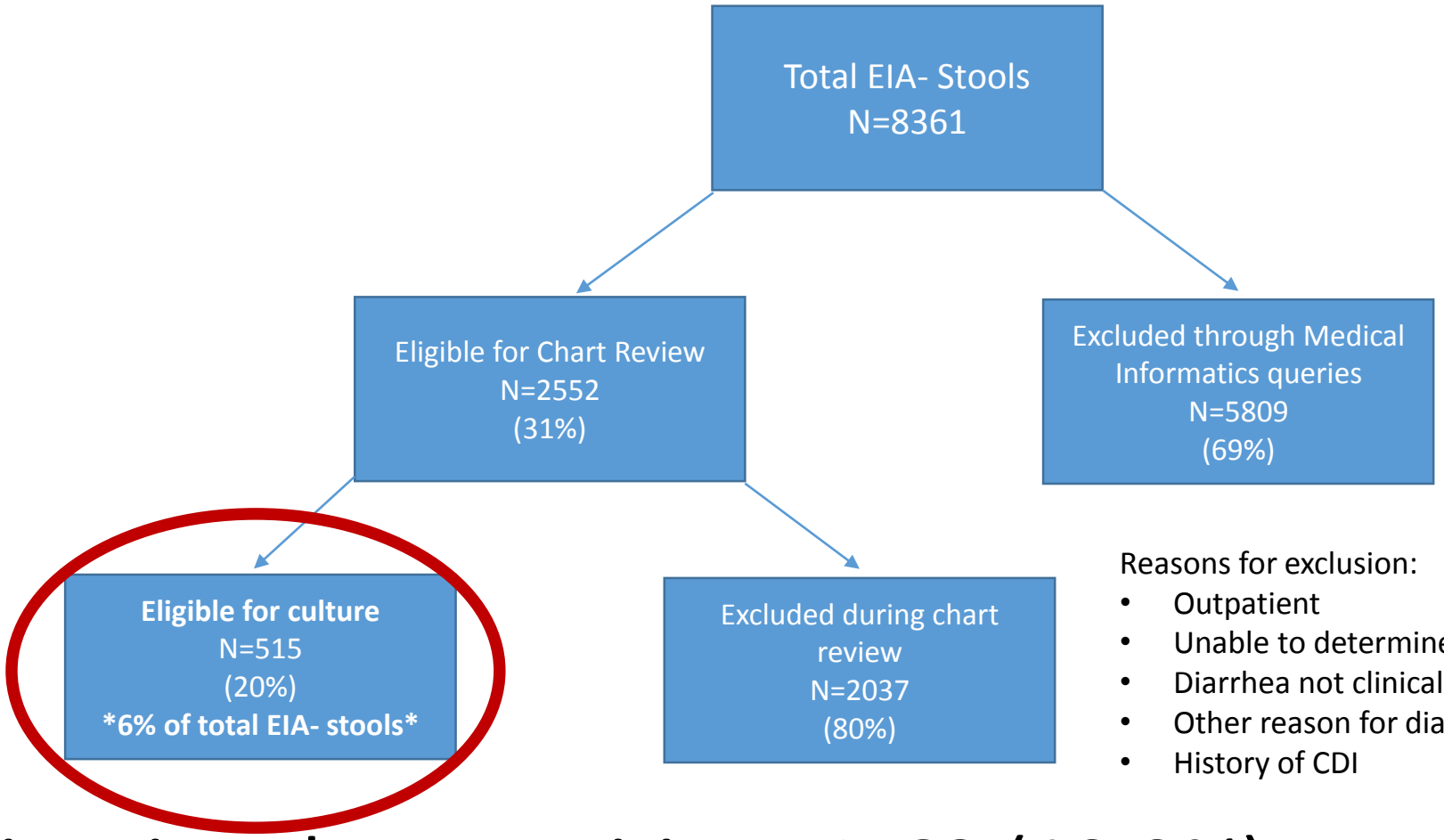
Both: weak recommendation, low quality of evidence

Will Limiting Testing to the “Ideal” World Limit False Positive NAATs for CDI?

- 2 years of data: 8,931 testing episodes
  - 8,361 EIA-
  - 570 EIA+

- Patients with
  - Clinically significant diarrhea (≥3 diarrheal BM/d or diarrhea plus abdominal pain)
  - No alternate explanation for diarrhea (e.g. laxatives, tube feeds, colostomy, etc.)
  - No recent CDI
  - For EIA-, no treatment for CDI
  - Inpatient

EIA- Stools



Reasons for exclusion:

- Medical condition associated with diarrhea
- Laxatives
- Tube feeds
- Ostomy
- Chemo
- Other infectious etiology
- History of CDI
- CDI treatment antibiotics

Reasons for exclusion:

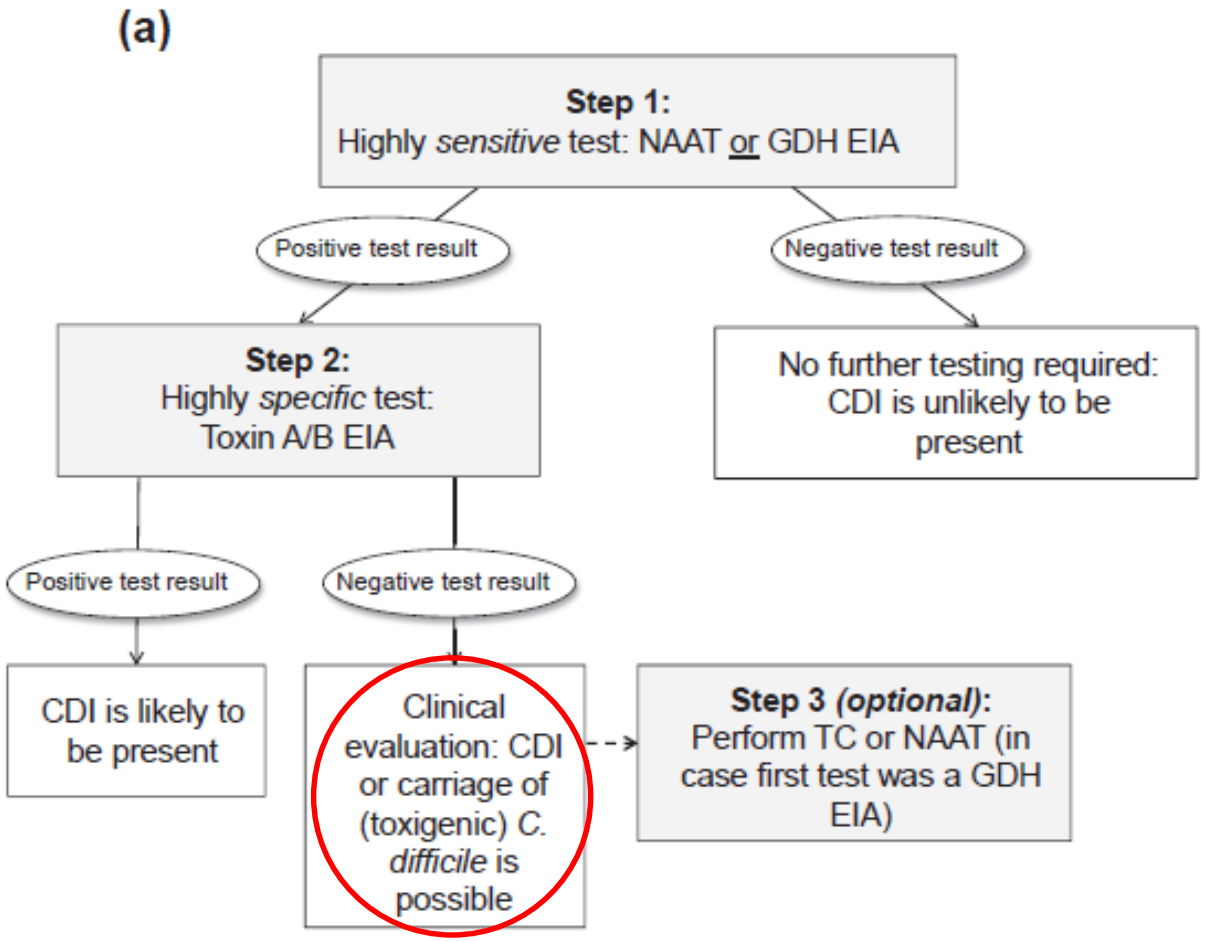
- Outpatient
- Unable to determine diarrhea severity
- Diarrhea not clinically significant
- Other reason for diarrhea
- History of CDI

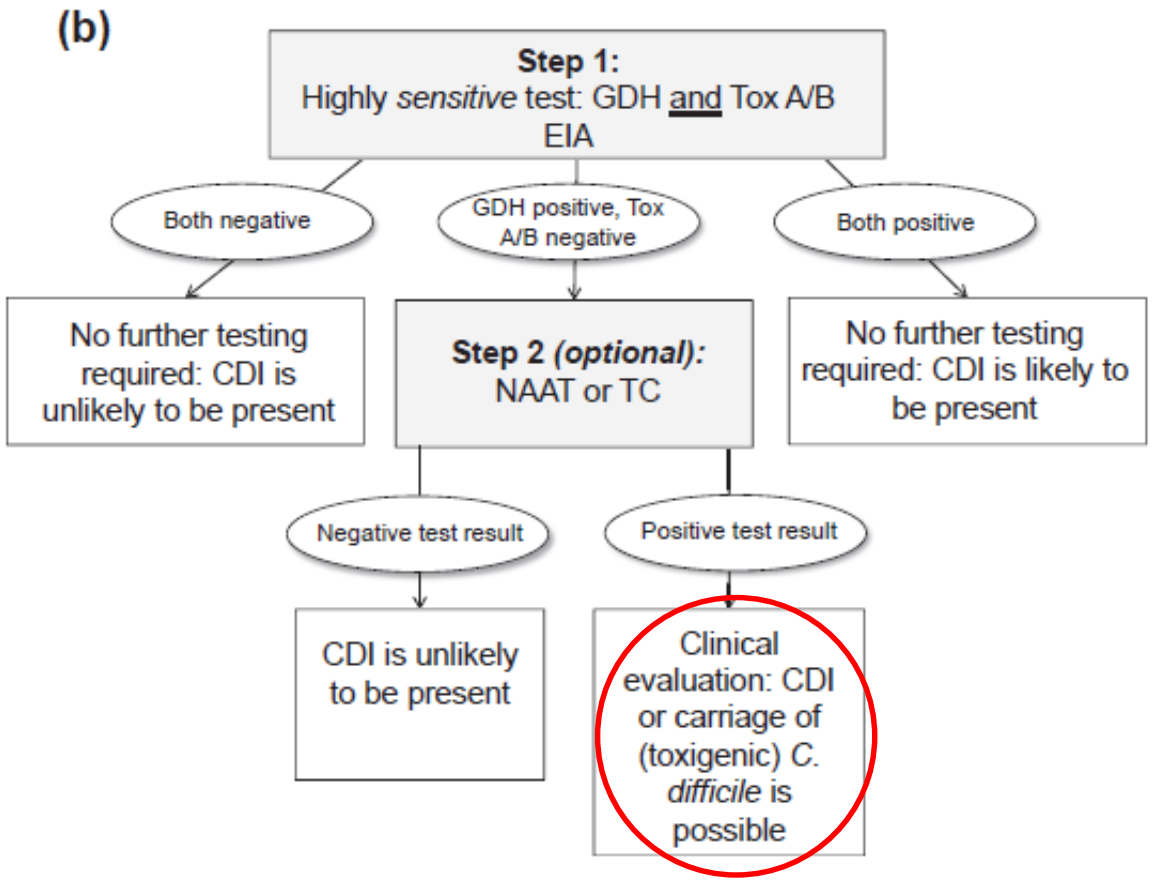
Toxigenic culture positive: N=63 (12.2%)

False Positives in Ideal World Testing Scenario

- Same process for EIA+ specimens
  - 107 (20%) met criteria
- 170 total that were EIA+ (107) or EIA- / toxigenic culture+ (63)
  - Most EIA- / toxigenic culture+ would be NAAT+
- If NAAT used: 63/170 = 37% false positives
  - Similar to what is seen in real world

European Recommendations: Importance of Toxin Detection and Clinical Evaluation





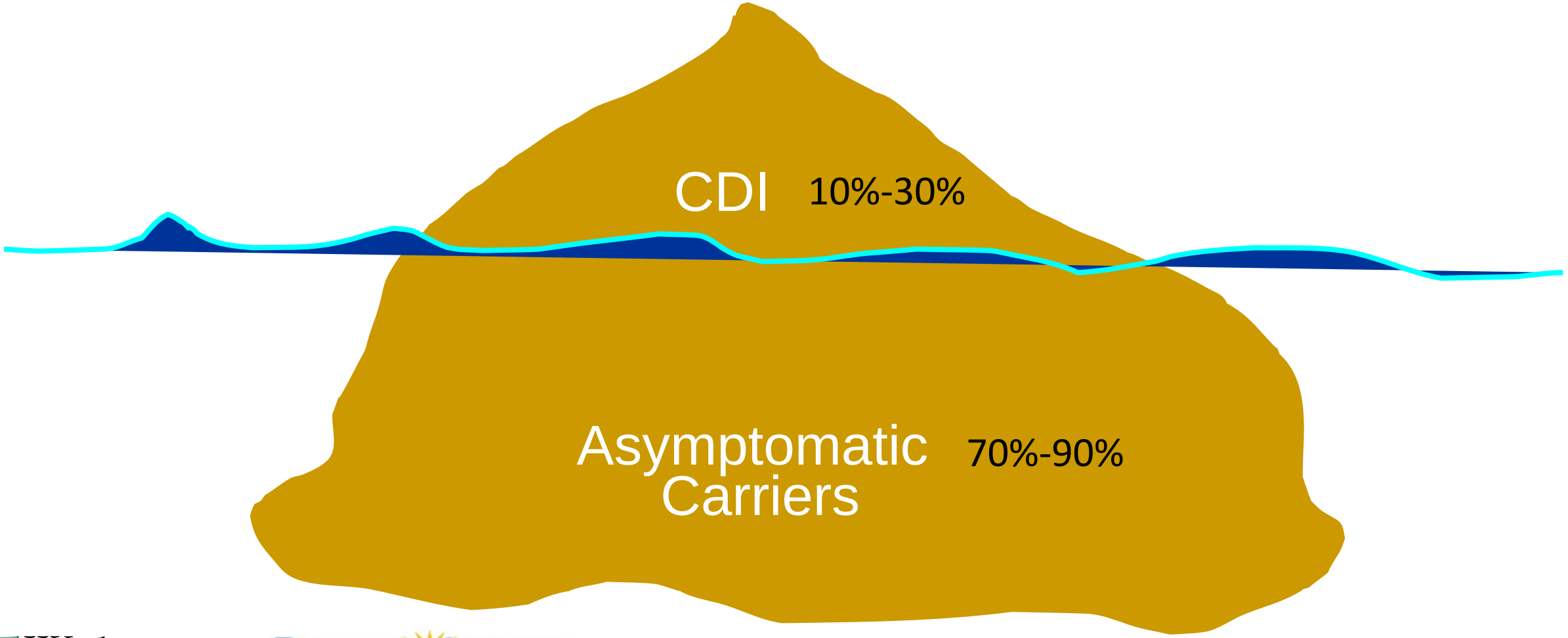
Crobach. Clin Microbiol Infect. 2016

Guidelines: Prevention

- Antimicrobial stewardship: best intervention available today
- Contact precautions: prevent transmission of *C. difficile* from patients with CDI
- Disinfecting the environment

- Screening for asymptomatic *C. difficile* carriers
  - Data not there to support recommendation
  - Needs more study

The *C. difficile* "Iceberg"



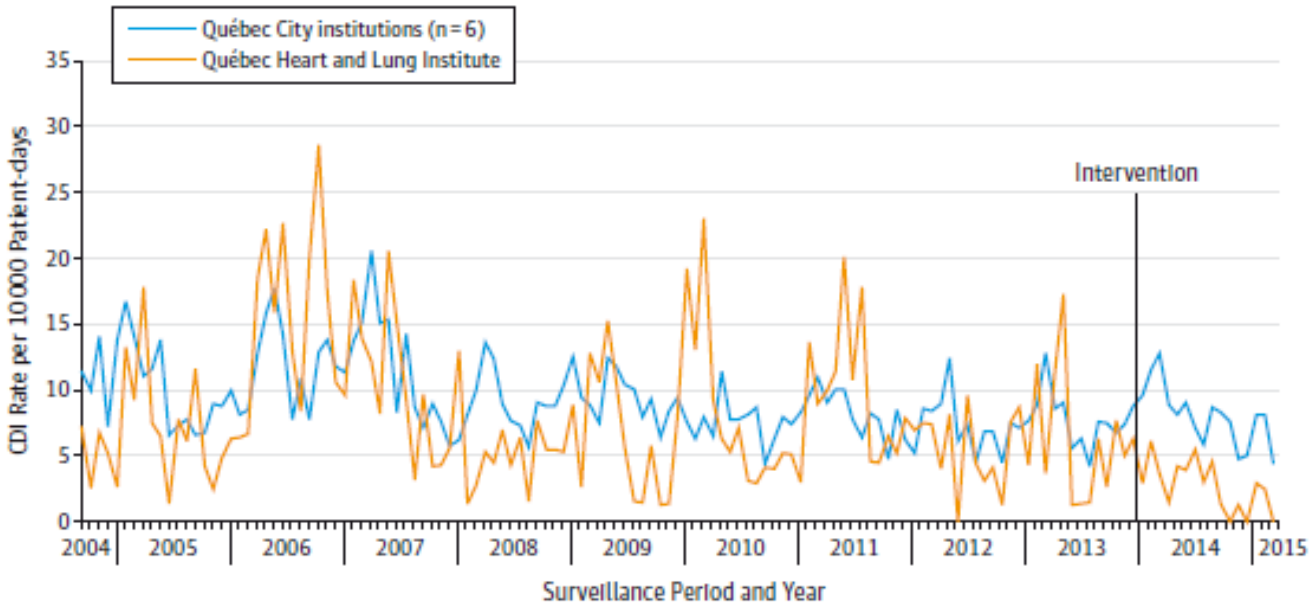
Courtesy L. Clifford McDonald (note: color changed from original slide)

Asymptomatic Carriers Contribute to CDI

- Clabots: 84% of new acquisitions came from an asymptomatic carrier
- Lanzas: at least 50% of hospital-onset CDI cases come from asymptomatic carriers
- Eyre: transmission from as few as 1% of asymptomatic carriers can account for 50% of CDI cases
- Curry: new hospital-onset CDI
  - 30% from other CDI cases
  - 29% from known asymptomatic carriers (not all patients screened)

Clabots. JID. 1992; Lanzas. ICHE. 2011; Eyre PLoS One. 2013; Curry. CID. 2013; McDonald. CID. 2013

Screening for Asymptomatic Carriage



- Issues to keep in mind
  - Single center
    - Recent abstract without significant reduction in CDI
  - Other potential explanations for reductions in CDI
    - More successful than models
  - Lessons learned from MRSA / VRE
  - Cost/expense/person-time to screen

Longtin. JAMA IM. 2016; Peterson. ECCMID. 2018. Abstract 2332; Lanzas. ICHE 2014

Guidelines: Treatment

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Initial episode

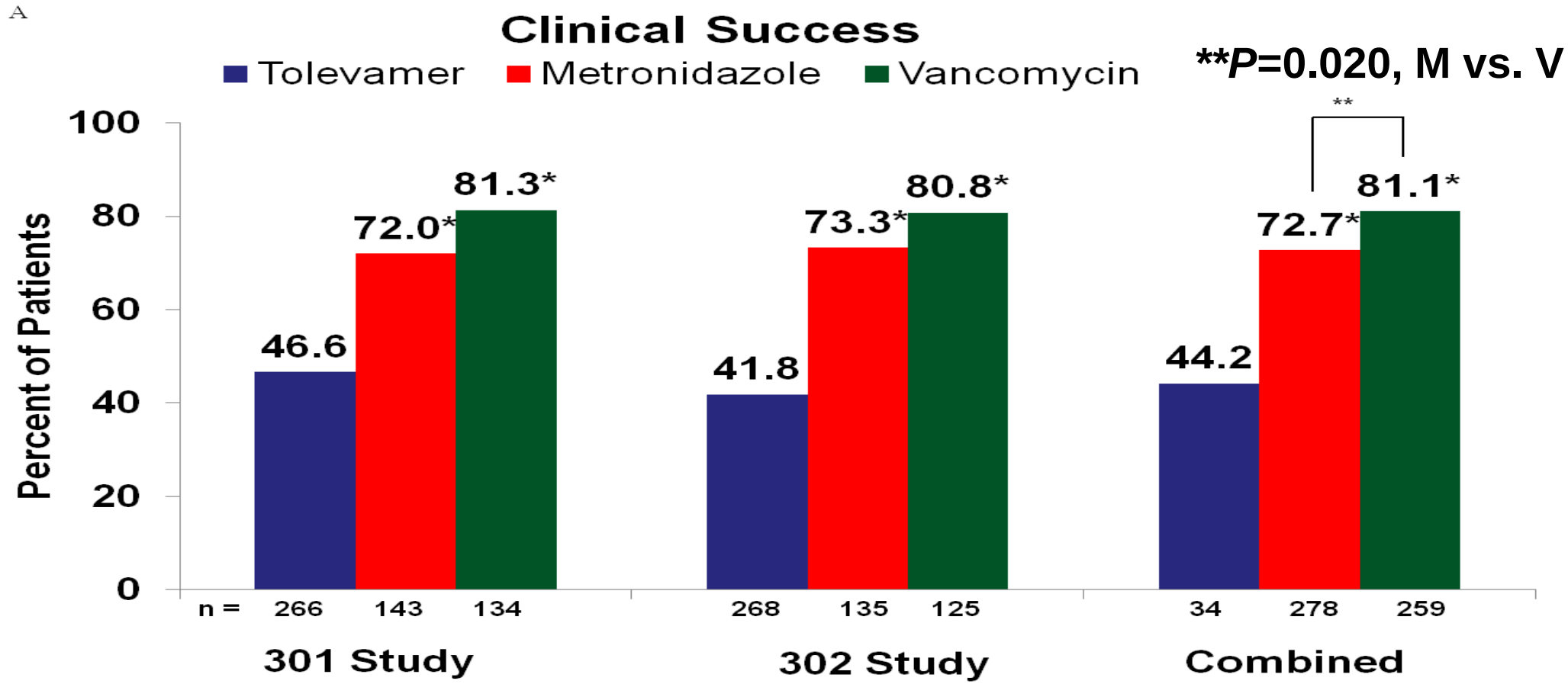
Clinical Definition	Supportive Clinical Data	Recommended Treatment (Strength of Recommendation/ Quality of Evidence)
Initial episode, non-severe	WBC ≤15,000 cells/ml, serum Cr <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days (Strong/High), OR • FDX 200 mg given twice daily for 10 days (Strong/High) • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days (Weak/High)
I severe	serum Cr >1.5 mg/dL	• VAN, 125 mg 4 times per day by mout r 10 days (Strong/High), OR • FDX 200 mg given twice daily for 10 da (Strong/High)
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mout r by nasogastric tube (Strong/Moderate). If ileus, consider ad g rectal instillation of VAN. IV metronidazole (500 mg every 8 hours) (S ong/Moderate) should be administered together with oral or recta AN (Weak/Low), particularly if ileus is present.

Fidaxomicin now first-line agent

Minor change to serum creatinine cut-off

Major change: metronidazole is no longer first line agent for non-severe CDI in settings where access to VAN/FDX is not limited

Metronidazole Inferior For Severe and Non-Severe CDI



Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-354.

Fidaxomicin vs. Vancomycin Clinical Outcomes in mITT Populations

- Novel macrocyclic antimicrobial
- Narrow spectrum
- No activity against Gram-negative agents
- Sparing of *Bacteroides* sp., *Bifidobacterium*, clostridial clusters IV and XIV

Clinical Outcomes	Fidaxomicin, n (%)	Vancomycin, n (%)	Treatment Difference	*P* Value
Clinical cure				
Louie[a]	253/287 (88.2)	265/309 (85.8)	-3.1*	
Cornely[b]	221/252 (87.8)	223/257 (86.7)	-4.9*	
Recurrence†				
Louie[a]	39/253 (15.4)	67/265 (25.3)	-9.9 (-16.6 to -2.9)	*P* =.0005
Cornely[b]	28/221 (12.7)	60/223 (26.9)	-14.2 (-21 to -6.8)	*P* =.0002
Sustained clinical response*				
Louie[a]	214/287 (74.6)	198/309 (64.1)	10.5 (3.1 to 17.7)	*P* =.006
Cornely[b]	193/252 (76.6)	163/257 (63.4)	13.2 (5.3 to 21)	*P* =.001

*Lower boundary 97.5% CI.
†95% CI.
a. Louie TJ, et al. *N Engl J Med*. 2011;364:422-431; b. Cornely OA, et al. *Lancet Infect Dis*. 2012;12:281-289.

Recurrence CDI

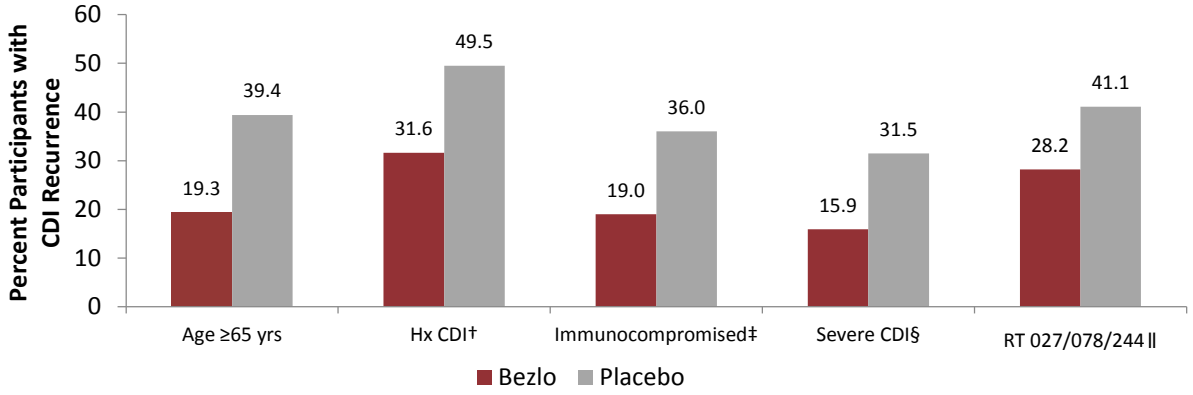
Clinical Definition	Recommended Treatment (Strength of Recommendation/ Quality of Evidence)
First recurrence	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode (Weak/Low), OR • Use a prolonged tapered and pulsed VAN regimen if a standar was used for the initial episode (Weak/Low), OR • FDX 200 mg given twice daily for 10 days if VAN was used for the initial Episode (Weak/Moderate)
Second or subsequent recurrence	• VAN in a tapered and pulsed regimen (Weak/Low), OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days (Weak/Low), OR • FDX 200 mg given twice daily for 10 days (Weak/Low), OR • Fecal microbiota transplantation (Strong/Moderate) (appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation)

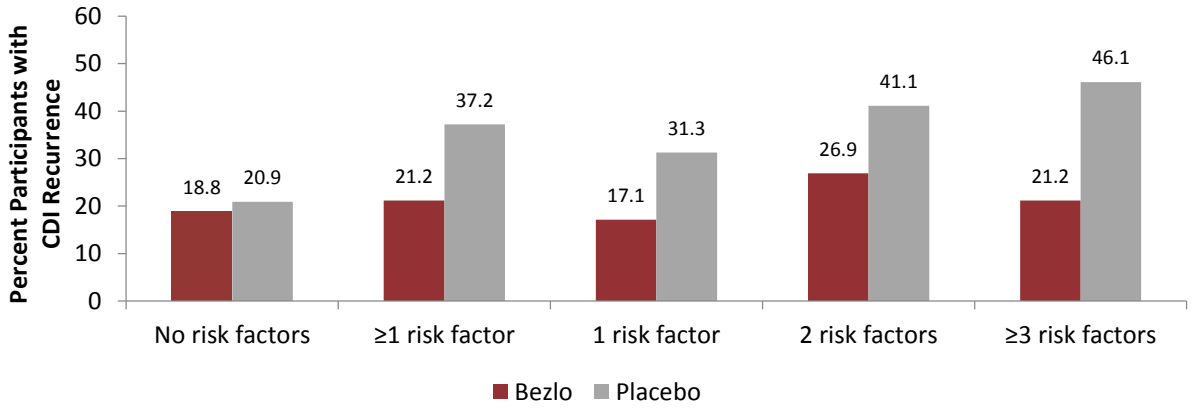
Do not give same regimen a second time

More options provided for second or subsequent recurrence

What about Bezlotoxumab?

- Monoclonal antibody against *C. difficile* toxin B
  - Administered as single IV infusion in addition to standard of care CDI treatment antibiotics
  - Indication: prevention of recurrent CDI
- Results not available early enough to be included





Gerding. CID. 2018

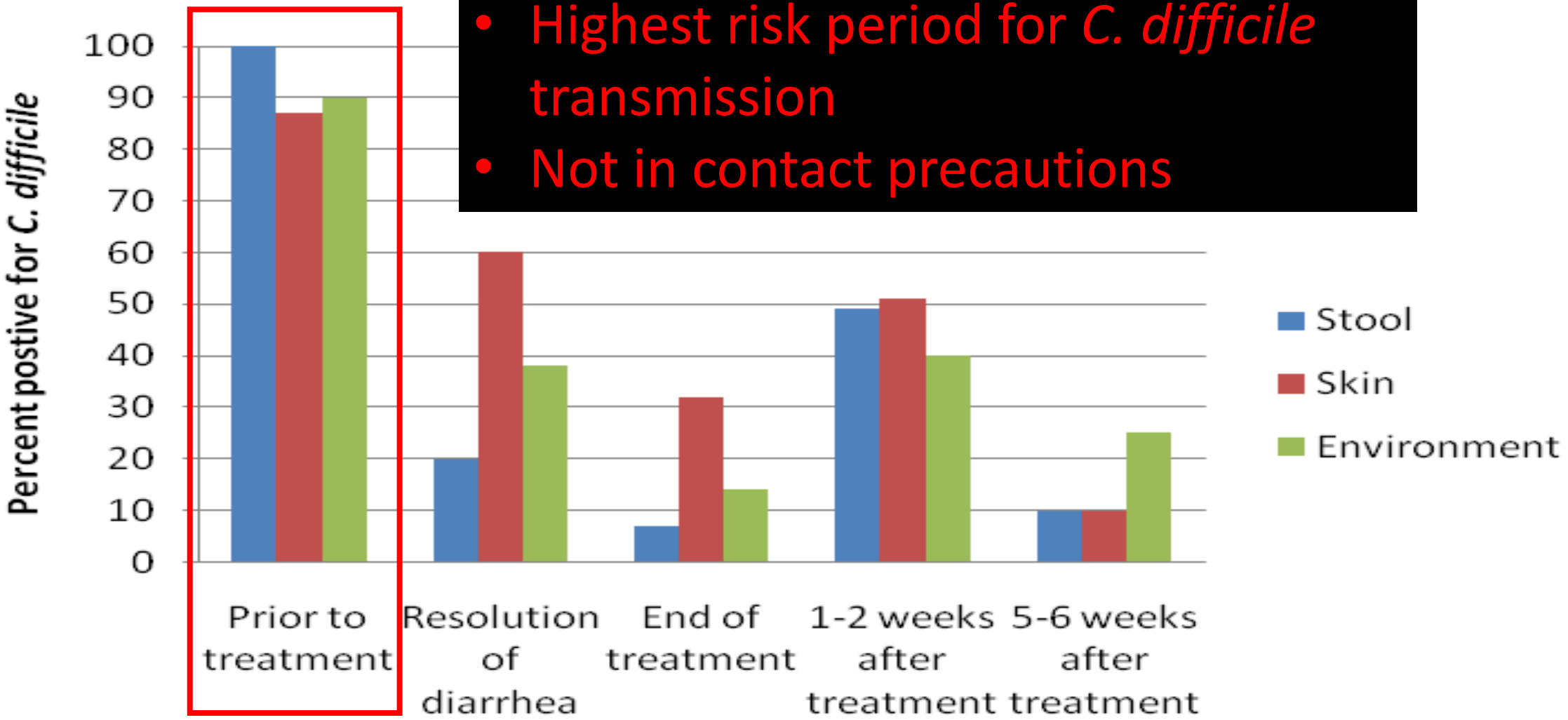
How Can the Microbiology Laboratory Help?

- CDI prevention multidisciplinary
  - Infection Prevention and Control
  - Antimicrobial Stewardship Program
  - Clinicians
  - Nurses
  - Housekeeping

- Microbiology laboratory: necessary piece
  - Time to diagnosis of CDI
  - Laboratory-based approaches to minimize false positives
  - Improve antimicrobial prescribing

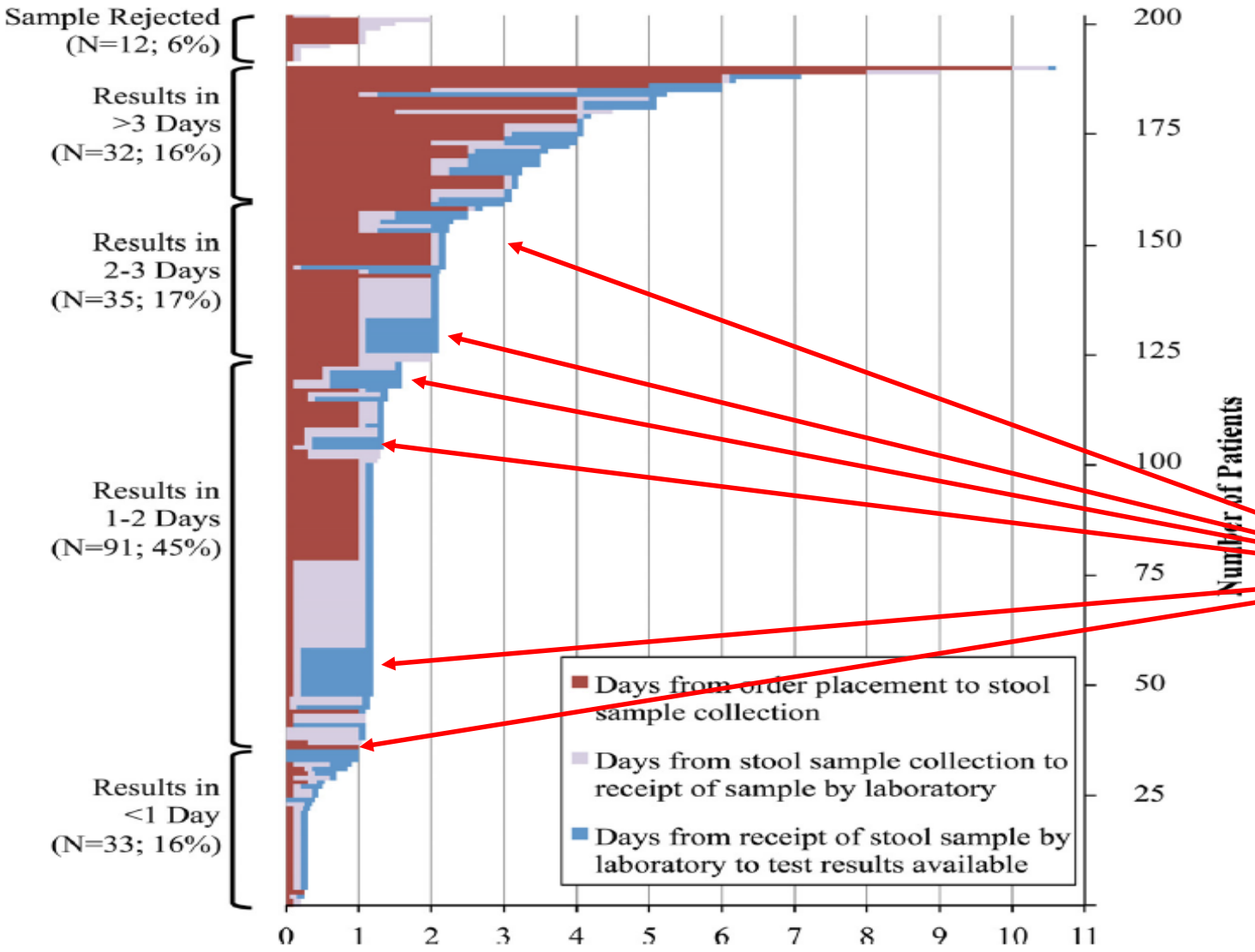
Greatest Risk of Transmission Early

- Highest risk period for *C. difficile* transmission
- Not in contact precautions



Sethi. ICHE. 2010

Potential Delays to Avoid



- Mean days from diarrhea onset to
  - Order: 1.4 days
    - Physician awareness
    - Nursing awareness
  - Result: 3.2 days
    - Time from order to collection
    - Frequency of testing

Kundrapu. JCM. 2013

Minimize False Positive Tests for CDI

- False positives lead to:
  - Unnecessary antimicrobial use
    - Promotes spread of resistant bacteria
    - Paradoxically may increase risk for CDI once stopped
  - Unnecessary contact precautions
    - Patient anxiety / satisfaction
    - Increase in adverse events
  - Lack of investigation for other causes of diarrhea
  - Diversion of limited resources
  - Masks impact of CDI prevention activities
  - Hospital may lose reimbursement from high CDI rates

Interventions to Minimize False Positive Tests

- DO NOT TEST FORMED STOOLS
  - No diarrhea = No CDI
- Do not allow test of cure
  - Not predictive of treatment success or risk of recurrent CDI
- Do not allow automatic repeat testing
  - Most positive tests on repeat testing are false positives
- Educate nurses and physicians on patient selection for testing
  - Diarrhea:
    - Clinically significant, no other cause: test ASAP (consider contact precautions)
    - Not clinically significant or alternate explanation (i.e. low pre-test probability): do not test
- Educate on test used at your facility
  - And always remind people: *C. difficile* test, NOT CDI test

Different Testing Strategies and False Positives

- Hypothetical scenarios
  - Toxin EIA: sensitivity 85%, specificity 97%
  - NAAT: sensitivity 99%, specificity 89% (CDI)
  - GDH: sensitivity 99% (ignore specificity)
  - Test 1,000 patients, 100 with CDI (10% prevalence)

Testing strategy	True positives	False positives
Toxin EIA only	85	27
NAAT only	99	99
NAAT or GDH (+) then Toxin EIA	84	3

Assist in Antimicrobial Stewardship

- Improve test utilization related to infections
  - Order of tests in drop down list
    - Most appropriate test first
  - Reflex urine cultures: >10 WBC / high power field
- Rapid diagnostics
  - MALDI
  - Rapid tests for resistance mechanisms
  - Respiratory multiplex PCRs

Barlam. CID. 2016; Sarg. ICHE. 2016; Subramony. J Pediatr. 2016

Conclusions: 2017 Guideline Update

- CDI epidemiology is changing
  - 027 strain may be declining
- Testing recommendations still with weak supportive data
  - Improve patient selection
  - In most scenarios, toxin testing helpful
- Antimicrobial stewardship best available CDI prevention intervention
  - Screening for asymptomatic carriage: research for now
- Major changes to treatment recommendations
  - Metronidazole no longer first-line agent
  - Fidaxomicin is a first-line agent
- The microbiology lab is a key component to CDI prevention efforts