Clostridium difficile Infection (CDI) Diagnosis, Treatment, and Prevention

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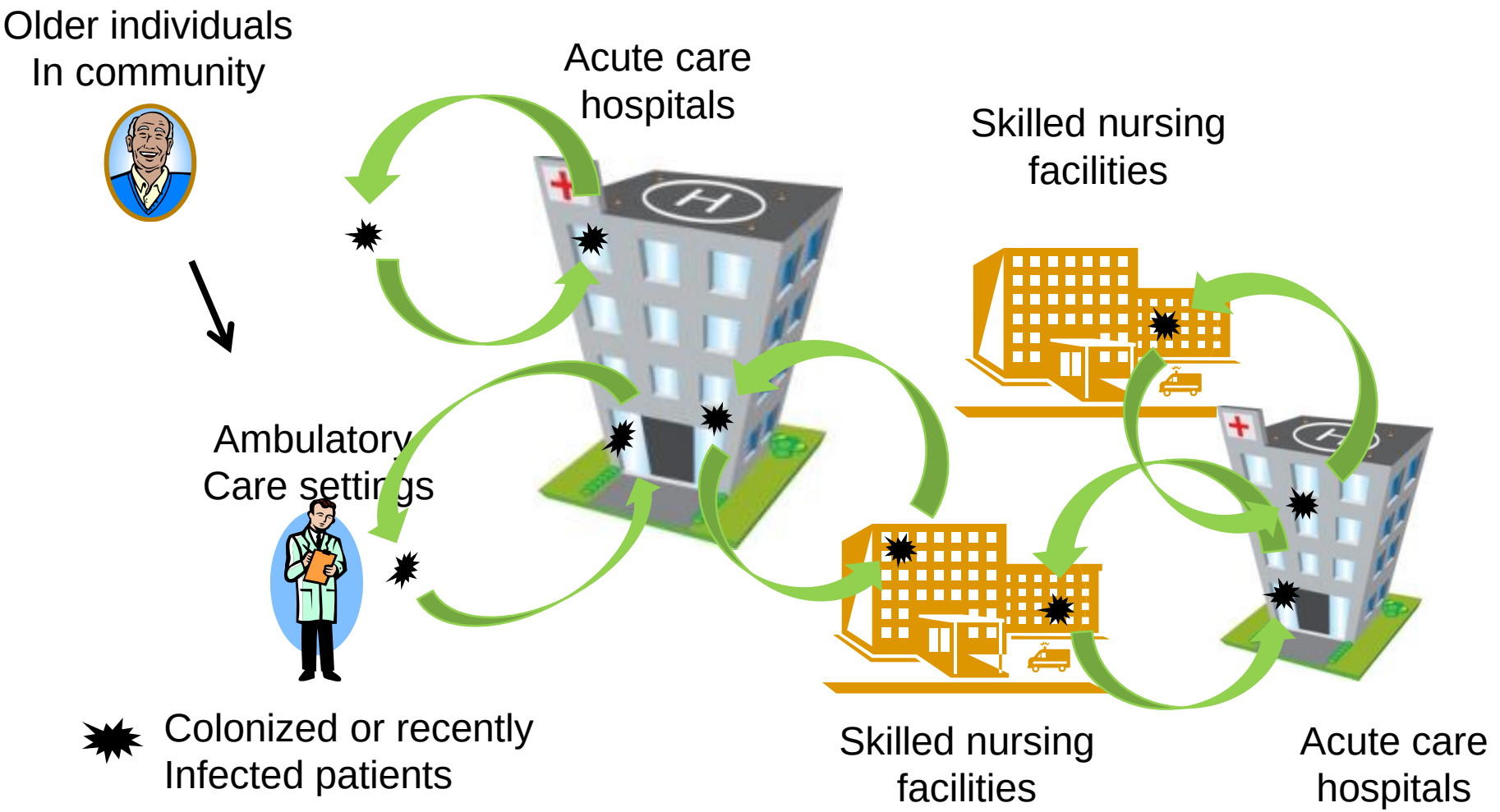
Agenda

- Epidemiology and transmission
- Diagnostic options
- Treatment
- Prevention

Epidemiology of C. *diff* Infections

Colonized and infected patients are links in the chain of transmission between neighboring healthcare settings



Burden of *Clostridium difficile* Infection in the United States

NAP 1 more prevalent among HA-CDI versus CA-CDI

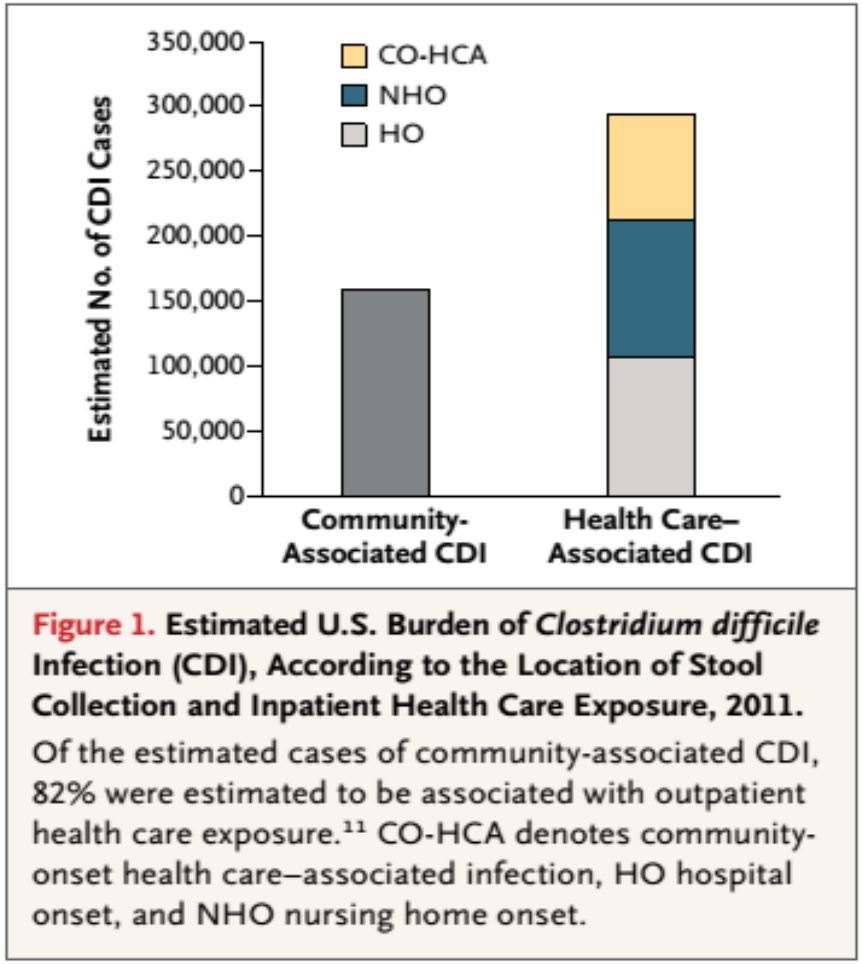
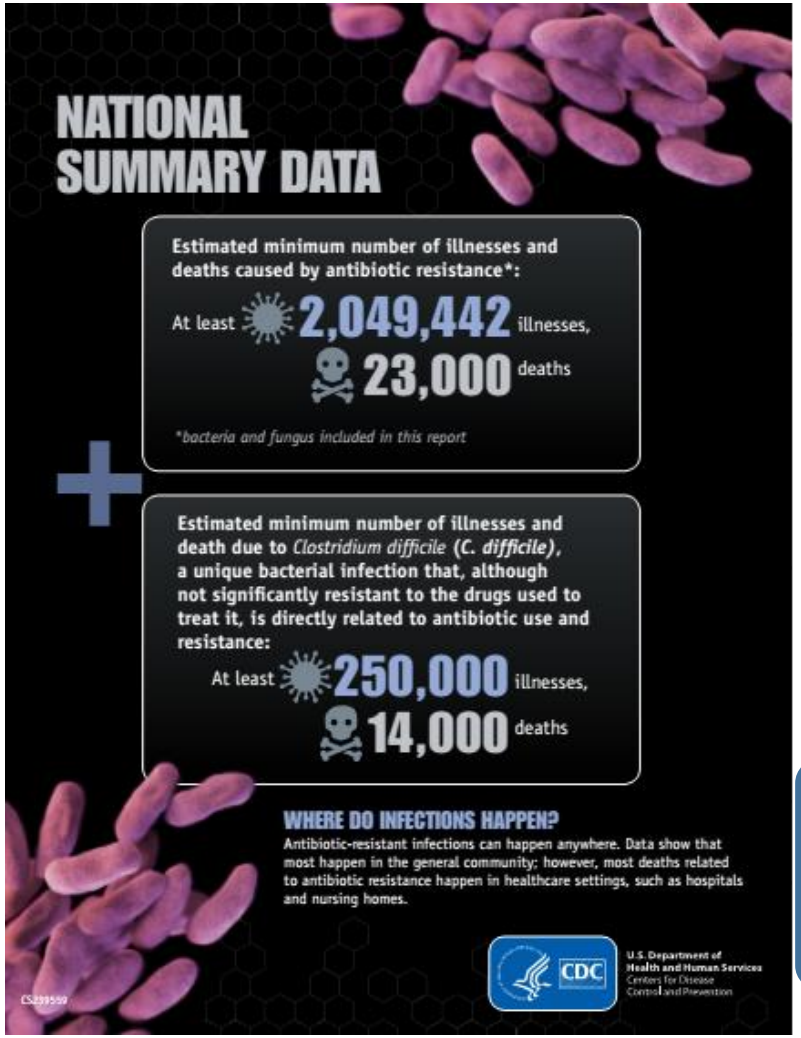


Figure 1. Estimated U.S. Burden of *Clostridium difficile* Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

Of the estimated cases of community-associated CDI, 82% were estimated to be associated with outpatient health care exposure.[11] CO-HCA denotes community-onset health care–associated infection, HO hospital onset, and NHO nursing home onset.

N Engl J Med 2015; 372:825-34

Burden of Clostridium *difficile* Infection in the United States



$20 billion in excess direct healthcare costs

Costs to society for lost productivity as high as $35 billion a year (2008 dollars)

The use of antibiotics is the single most important factor leading to antibiotic resistance

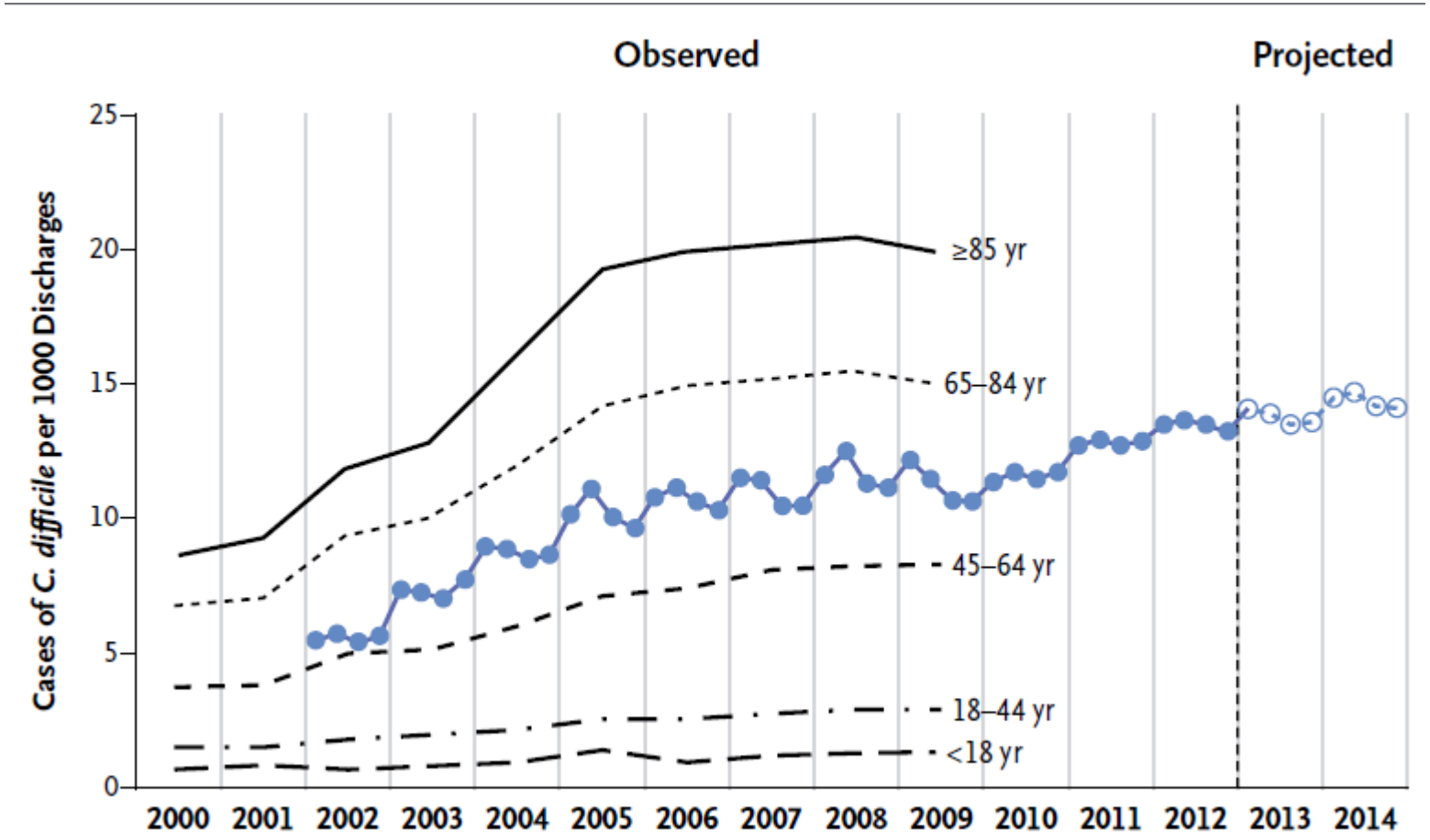
↑ **C. *difficile* infections** [1]

453,000 case 2011

29,000 deaths 2011

N Engl J Med 2015; 372:825-834

CDI Incidence (HA)



N Engl J Med 2015; 372:1539-1548

HAI and Cost

HAI Infections[1] (percent)	Estimated Costs[2] ($)	LOS[2] (days)
Pneumonia (21.8)†	40,144(VAP)	13.1
Surgical-site infection (21.8)	20,785	11.2
GI infection ‡ (17.1)	11,285(C. diff)	3.3
UTI(12.9)¥	896 (CAUTI)	Not reported
Primary BSI (9.9)§	45,814 (CLABSI)	10.4

† 39.1 % associated with mechanical ventilation

‡ 70.9% *C. difficile*

¥ 67.7 % associated with a catheter

§ 84% associated with a central catheter

Annual cost 9.8 billion

Top 5 HAIs [2]

1. *N Engl J Med* 2014; 370:1198-1208
2. *JAMA Intern Med* 2013; 173:2039-2046

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multistate Point-Prevalence Survey of Health Care–Associated Infections

Shelley S. Magill, M.D., Ph.D., Jonathan R. Edwards, M.Stat.,
Wendy Bamberg, M.D., Zintars G. Beldavs, M.S.,
Marion A. Kainer, M.B., B.S., M.P.H., Ruth Lynfield, M.
Laura McAllister-Hollod, M.P.H., Joelle Nadle, M.
Deborah L. Thompson, M.D., M.S.P.H., L.
and Scott K. Fridkin, M.D., for the Emergin
Healthcare-Associated Infections and Antimicrobial

Pathogen	All Health Care–Associated Infections (N = 504)†	
	no. (%)	*rank*
Clostridium difficile	61 (12.1)	1
Staphylococcus aureus	54 (10.7)	2
Klebsiella pneumoniae or *K. oxytoca*	50 (9.9)	3
Escherichia coli	47 (9.3)	4
Enterococcus species‡	44 (8.7)	5
Pseudomonas aeruginosa	36 (7.1)	6
Candida species§	32 (6.3)	7
Streptococcus species¶	25 (5.0)	8
Coagulase-negative staphylococcus species	24 (4.8)	9
Enterobacter species	16 (3.2)	10

CDC Metrics in Action Plan

Infection	Baseline Period	5-Year Target	Metric Measure	Target SIR or Rate
Central Line-Associated BSI	2006-08	50% reduction	SIR	0.50
Catheter-Associated UTI	2009	25% reduction	SIR	0.75
Surgical Site Infection	2006-08	25% reduction	SIR	0.75
MRSA Bacteremia (Hospital-based)	2010-11	25% reduction	SIR	0.75
Invasive MRSA Infections (Population-based)	2007-08	50% reduction	Rate	13.5 per 100,000 population
C. *difficile* Infections	2010-11	30% reduction	SIR	0.70

2013 HHS Update

HAI TYPE	# OF U.S. HOSPITALS THAT REPORTED DATA TO CDC'S NHSN, 2013+	2013 NAT'L SIR vs. 2012 Nat'l SIR‡	2013 NAT'L SIR vs. Nat'l Baseline‡	2013 NAT'L SIR
CLABSI Nat'l Baseline: 2008	3,578	↓ 4%	↓ 46%	0.54
CAUTI Nat'l Baseline: 2009	3,640	↑ 3%	↑ 6%	1.06
SSI, Abdominal Hysterectomy Nat'l Baseline: 2008	3,182	⇩ 4%	↓ 14%	0.86
SSI, Colon Surgery Nat'l Baseline: 2008	3,348	↑ 14%	↓ 8%	0.92
MRSA Bacteremia Nat'l Baseline: 2011	3,827	↓ 5%	↓ 8%	0.92
***C. difficile* Infections** Nat'l Baseline: 2011	3,924	↓ 6%	↓ 10%	0.90

CDI Pathophysiology & Risk Factors

Microbiology

- Ubiquitous anaerobic, Gram-positive, spore-forming rod
- Common cause of antibiotic-associated diarrhea
- Can produce toxins causing colitis
- Associated with extended hospital stay and increased resource utilization
- When the normal gastrointestinal (GI) flora is disrupted, exposure to C. *difficile* may result in CDI
- Colonization Rates
  - **Healthy adults: 3%–5%**
  - **Inpatients: 16%–35%**

Lancet Infect Dis. 2005;5:549-557.
Med Clin North Am. 2006;90:1141-1163.

Risk Factors

Broad-spectrum antibiotic use

Hospitalization

Age > 64 years

Long-term care facility (LTCF)

Gastrointestinal surgery

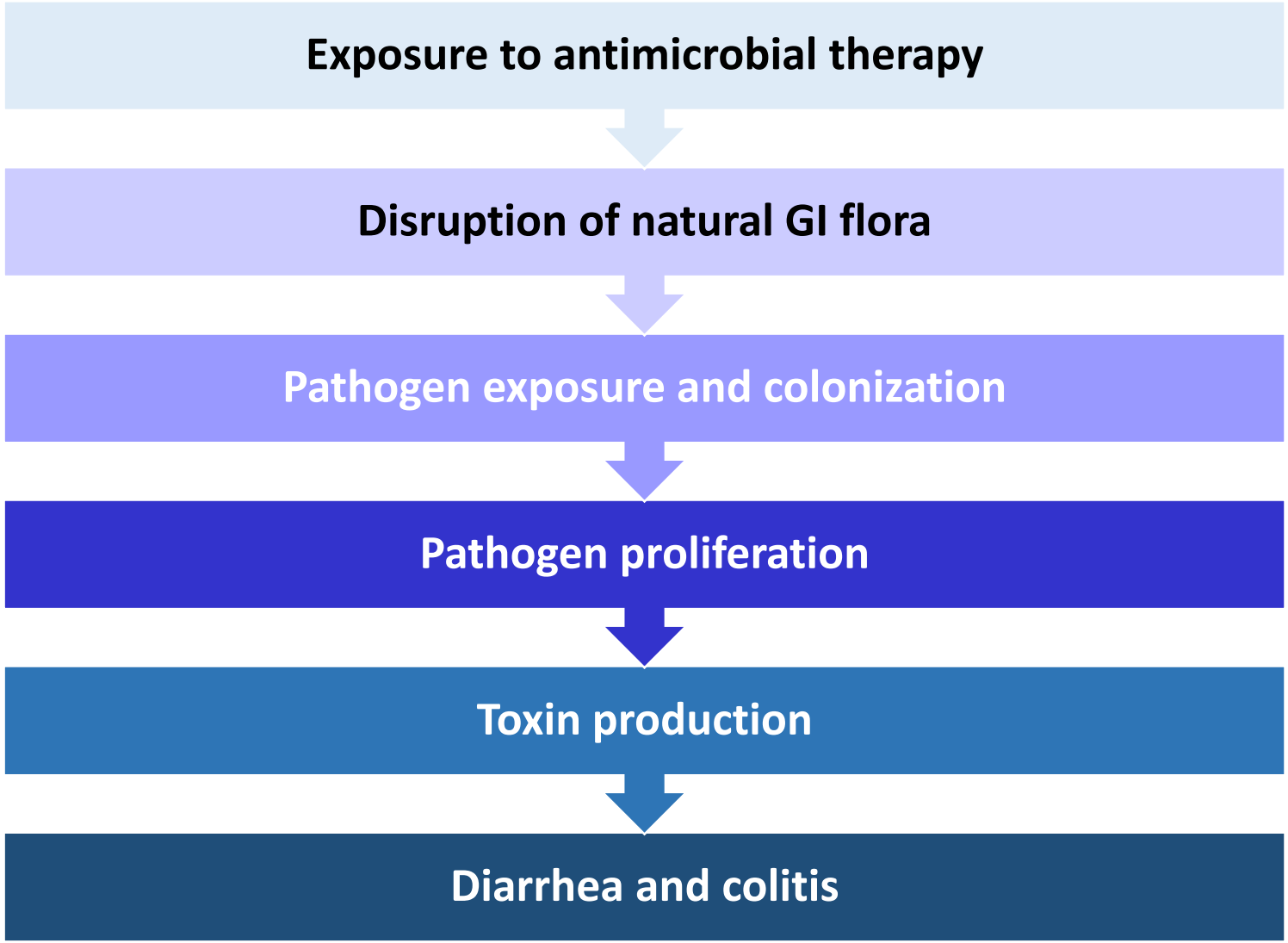
Inflammatory bowel disease

Immunosuppression

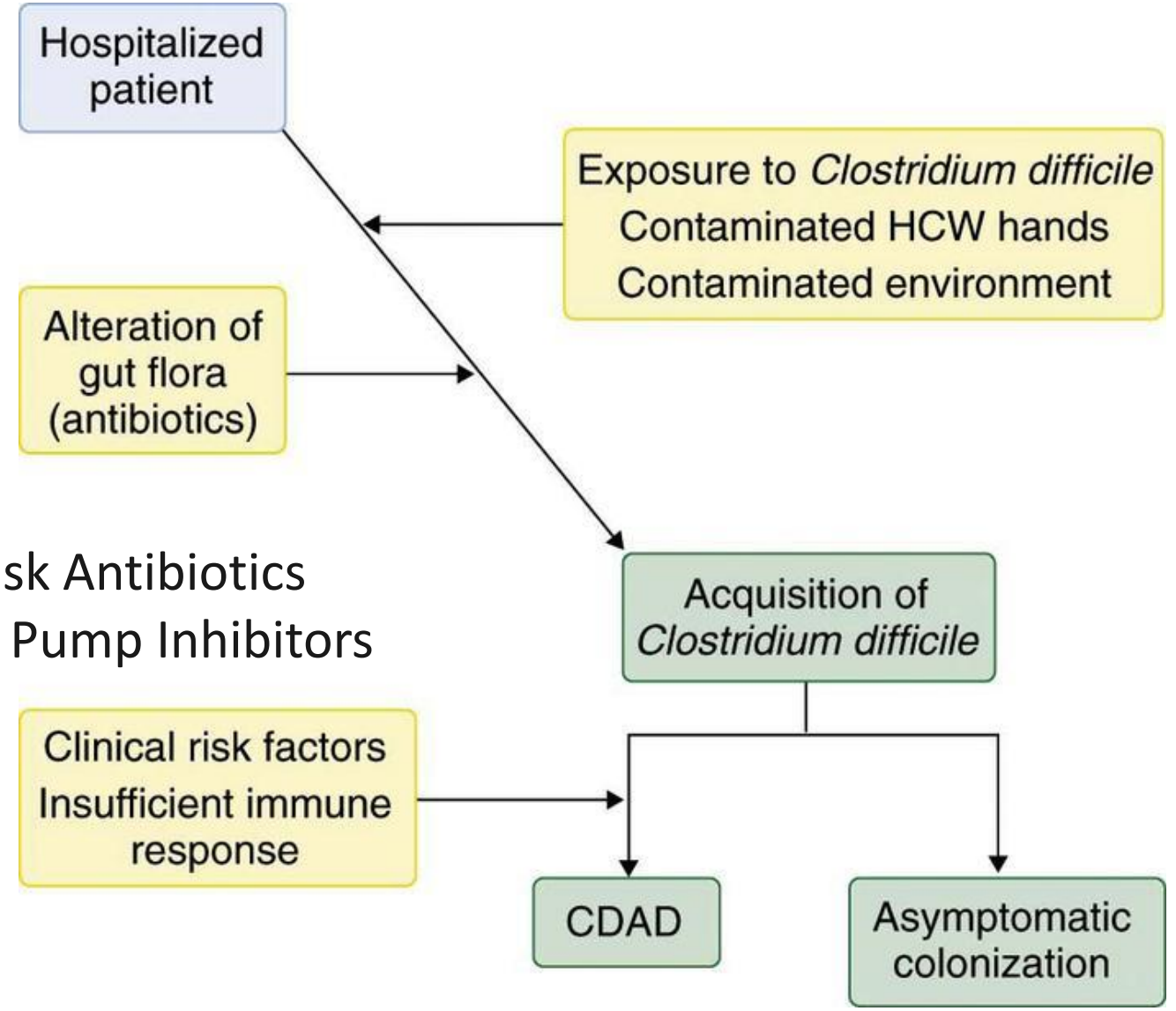
Proton-Pump Inhibitors

Pharmacotherapy. 2006; 26(3): 299-311.

Pathophysiology



Transmission of *C. difficile*



High Risk Antibiotics
Proton Pump Inhibitors

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/infectious-disease/clostridium-difficile-infection/images/clostridium-fig1_large.jpg

Antibiotic Classes and Their Association with *Clostridium difficile* Infection

Class	Association with *C. difficile* Infection
Clindamycin	Very common
Ampicillin	Very common
Amoxicillin	Very common
Cephalosporins	Very common
Fluoroquinolones	Very common
Other penicillins	Somewhat common
Sulfonamides	Somewhat common
Trimethoprim	Somewhat common
Trimethoprim–sulfamethoxazole	Somewhat common

N Engl J Med 2015; 372:1539-1548

Diagnosis

Two questions:
1. What are the clinical characteristics that best identify a patient to test for *C. diff*?
2. What test or combination of tests best identifies patients who are symptomatically infected with toxigenic *C diff?*

Clinical Manifestations

- Symptoms range from diarrhea to fulminant and/or fatal pseudomembranous colitis
- Diarrhea may be associated with the passage of mucus or occult blood in the stool
- Fever, dehydration, cramping, abdominal discomfort, and leukocytosis are also common

Diagnosis

Per IDSA/ASM/SHEA guidelines, CDI is considered a combination of the following:

Presence of diarrhea

- *defined as passage of ≥3* ***unformed*** *stools in ≤24 hours*

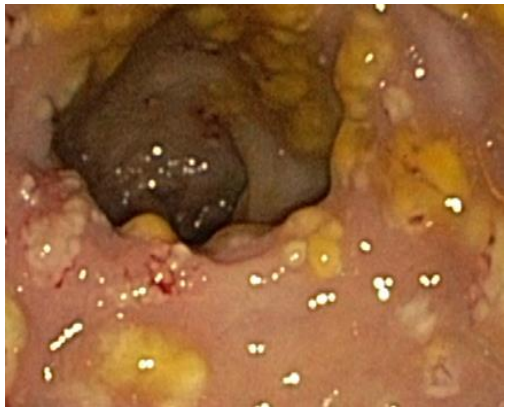
A stool test result positive for the presence of toxigenic *C. difficile* or *positive for* toxin-coding genes by NAAT

and/or colonoscopic findings demonstrating pseudomembranous colitis

C. difficile is the only pathogen known to cause pseudomembranous colitis

Despite negative microbiological findings, CDI can be diagnosed definitively by colonoscopic evidence of pseudomembranous colitis

Other findings include toxic megacolon and ileus



Pseudomembranous colitis visualized by colonoscopy

IDSA = Infectious Disease Society of America
ASM = American Society for Microbiology
SHEA = Society for Healthcare Epidemiology of America

Diagnostic Testing

Only stool from patients with diarrhea should be tested

Specimen should assume the shape of the container

Discourage repeat testing

Test of cure is NOT recommended

If the stick stands the test is **BANNED**

ICHE. 2010; 31(5): 431-55.
AJG 2013;108:478.
Clinical Microbiology Procedures Handbook 2010

Microbiological Diagnosis

Tests for GDH antigens (detects carriage)

- Glutamate dehydrogenase (GDH)

Tests for *C. difficile* toxins (toxin assays)

- Enzyme immunoassay (EIA) for toxins A and B

Combo test combines both assays (GDH and tests for toxins) on a single platform

Molecular testing (nucleic acid amplification/PCR) for toxin- coding genes

Culture

- Not usually performed outside of research settings

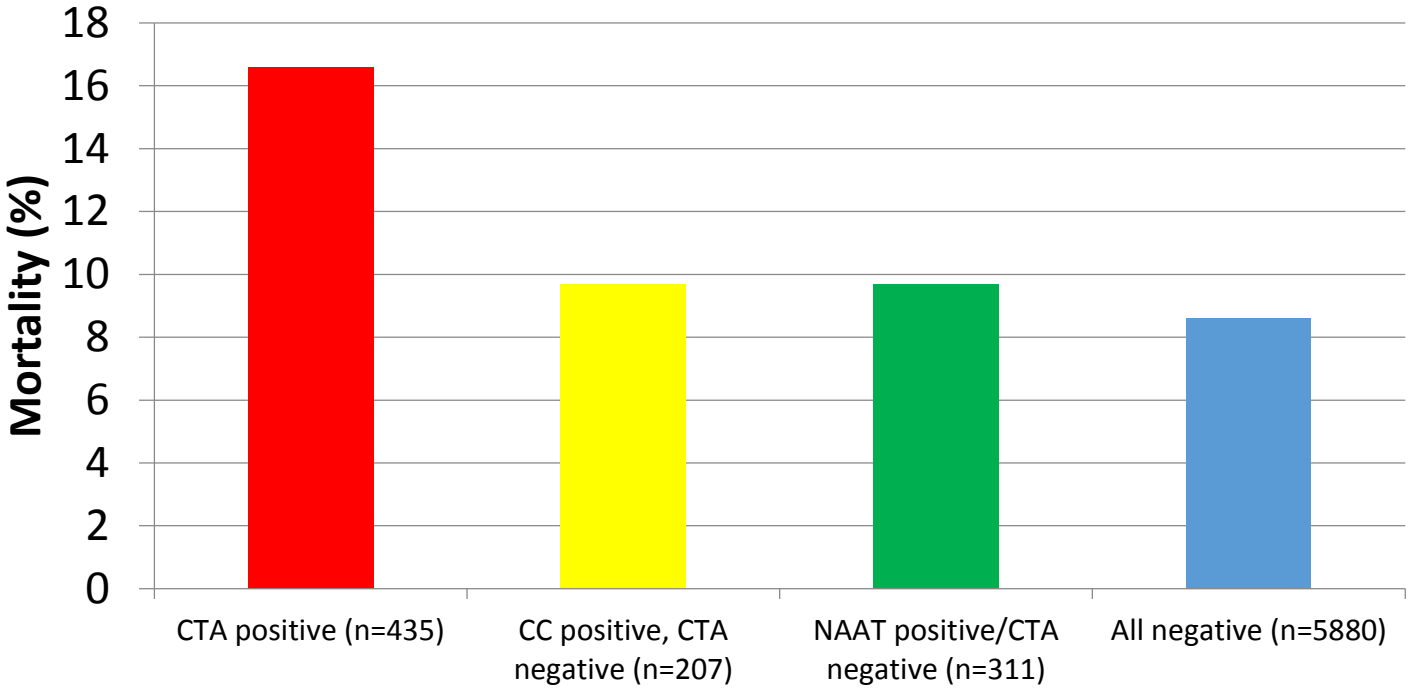
Tests to Establish a Diagnosis

Test or Procedure	Result Suggesting CDI	Comments	Sensitivity	Specificity
Glucose dehydrogenase	Negative test effectively rules out CDI	Positive samples should be confirmed using a second assay to discern toxin producing strains	High	Low
Fecal enzyme immunoassay test for toxin A or toxin B or both	Positive test	Rapid and available for all laboratories; method may miss up to 30% of true positives, confirm negatives with a second assay	Low	High
Combination GDH and Toxin A&B test by EIA	Positive GDH with Positive Toxin	**Rapid Combo EIA assay available on single platform** Confirm GDH positive Toxin negatives with a second assay	**High**	**High**
PCR (NAAT)	Positive test	Test for toxin genes (not toxin) that is very sensitive; **may not always differentiate between asymptomatic carriers and cases of CDI**	High	Mod-High
Cell culture cytotoxicity	Positive test with neutralization using anti- *Clostridium* toxin antibodies	Takes several days and is available **only in research laboratories**	High	High
Fecal toxigenic culture for *C difficile*	Positive with confirmation that the strain has genes for toxin(s)	Takes several days and is available **only in research laboratories**	High	High
Colon endoscopy (flexible sigmoidoscopy or colonoscopy)	Necessary to confirm of pseudomembranous colitis	This is not normally needed in CDI cases	Moderate	High
Abdominal CT scan	Patients with CDI often show colonic mucosal swelling	Finding a positive CT scan shows moderate sensitivity and high specificity and has prognostic significance in a patient clinically suspected as having CDI	Moderate	High

Modified Dupont HL. CGH 2013;11:1216.

PCR diagnostic strategies may detect patients colonized with CDI but not infected

UK: prospective, multicenter study of suspected CDI patients tested for cytotoxicity assay (CTA), cytotoxigenic culture (CC), or nucleic acid amplification test (NAAT).



Mortality increased significantly in CTA positive patients (OR 1·61, 95% CI 1·12–2·31)

Lancet Infect Dis 2013;13:936-45

C. difficile Testing

Testing Option	Result	Interpretation
EIA Toxin Test (A&B)	Toxin Pos (high specificity)	**Presume CDI**
EIA Toxin-No longer recommended as stand alone test	Toxin Neg (low sensitivity)	Perform PCR/NAAT
GDH and Toxin A&B Combo Test	GDH Neg (high sensitivity)	**No CDI, no further testing**
	GDH Pos, Toxin Pos	**Presume CDI**
	GDH Pos, Toxin Neg (GDH has low specificity)	Perform PCR/NAAT
PCR/NAAT *(Illumigene, Cepheid, BD GenProbe)*	PCR/NAAT Pos (high sensitivity but only mod specificity, does not distinguish true CDI from asymptomatic carriers)	CDI or possible carriage; perform clinical assessment
	PCR/NAAT Neg	**No CDI, no further testing**

- **Test only liquid specimens that conform to shape of the cup (except ileus)**
- **PPV dependent upon disease prevalence**
- **Test methods with higher sensitivity and PPV reduces repeat testing**

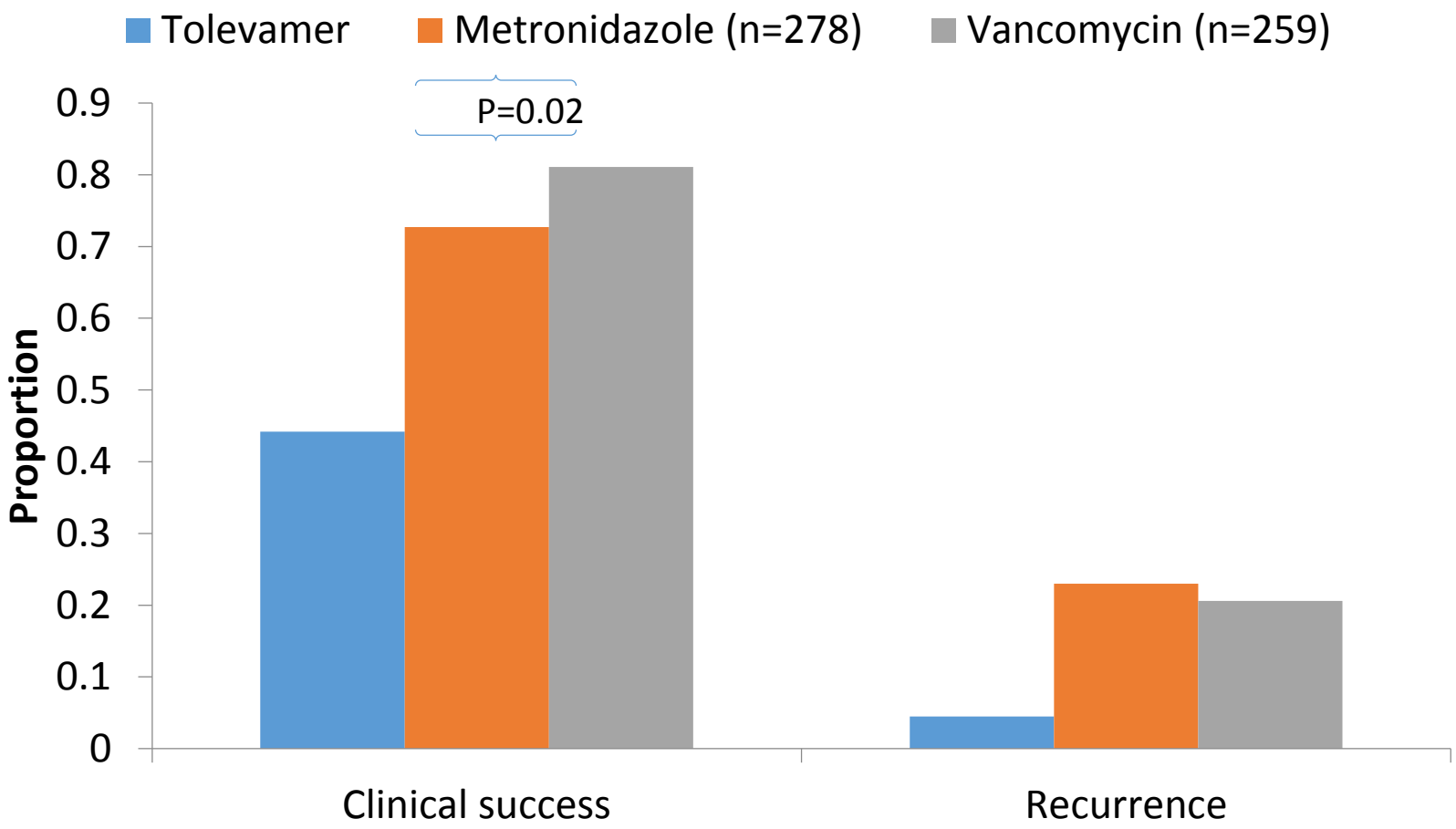
Management

Stratification by Severity

Severity	Clinical Manifestations
Asymptomatic carrier	No symptoms or signs
Mild	Mild diarrhea (3 to 5 unformed bowel movements per day), afebrile status, mild abdominal discomfort or tenderness, and no notable laboratory abnormalities
Moderate	Moderate non-bloody diarrhea, moderate abdominal discomfort or tenderness, nausea with occasional vomiting, dehydration, white-cell count >15,000/mm^3, and blood urea nitrogen or creatinine levels above baseline
Severe	Severe or bloody diarrhea, pseudomembranous colitis, severe abdominal pain, vomiting, ileus, temperature >38.9°C, white-cell count >20,000/mm^3, albumin level <2.5mg/dl, and acute kidney injury
Complicated	Toxic megacolon, peritonitis, respiratory distress, and hemodynamic instability

N Engl J Med 2015;372:1539-1548

Metronidazole has been shown to be globally inferior to vancomcyin



Clin Infect Dis. 2014;59:345-354

Newest Antimicrobial for CDI: *Fidaxomicin*

- Fidaxomicin
  - Nonabsorbed macrocyclic compound, narrower spectrum than vancomycin
  - Approved for use in CDI in 2011

Outcome	Fidaxomicin (n = 287)	Vancomycin (n = 309)	*P* value
4-week recurrence	15.4%	25.3%	*P*=.005
Global cure	74.6%	64.1%	*P*=.006
Global cure B1/NAP1	78.7%	80.7%	*P=NS*

Louie TJ, et al. *N Engl J Med*. 2011;364:422-431.

First Episode

- Mild-to-Moderate:
  - ?Metronidazole 500 mg orally 3 times a day for 10-14 days or
  - Vancomycin 125 mg orally 4 times a day for 10-14 days
- Severe:
  - Vancomycin 500 mg orally 4 times a day for 10-14 days
- Complicated:
  - Consider combination of metronidazole 500 mg intravenously 3 times a day and vancomycin 500 mg orally 4 times a day

- N Engl J Med 2015; 372:1539-1548

First Recurrence

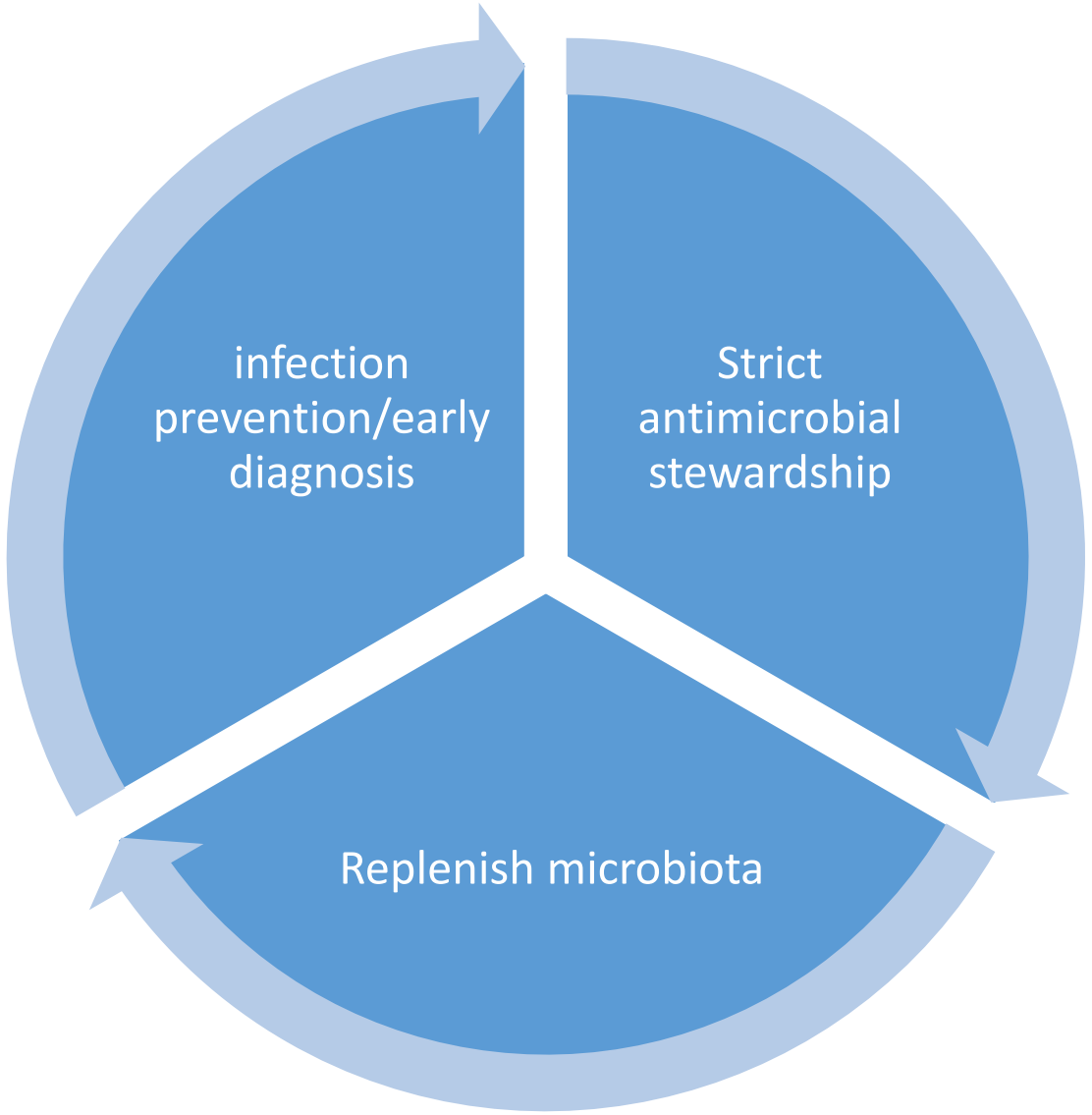
- Observed recurrence rates: 20-30%
- Treatment is usually with the same agent(s) as the initial episode
  - Stratification by severity still necessary
  - Treat for 14 days

Further Recurrence

- Avoid metronidazole due to potential for neurotoxicity
- Can be managed with ORAL vancomycin therapy using a tapered and/or pulse regimen
- Fidaxomicin may be an option for specific patient situations after consultation with ID or GI experts
- Fecal microbiota transplant (FMT) can be considered in refractory cases, see FDA guidance for more information

Prevention

The Bundled Approach to CDI



Emerg Microbes and Infect 2014;3:e43

Infection Prevention Strategies and Interventions

- Infection prevention and stewardship
- Burden of *C. difficile*
- Early detection and management of infections
- Precautions to prevent transmission

C. difficile Prevention:

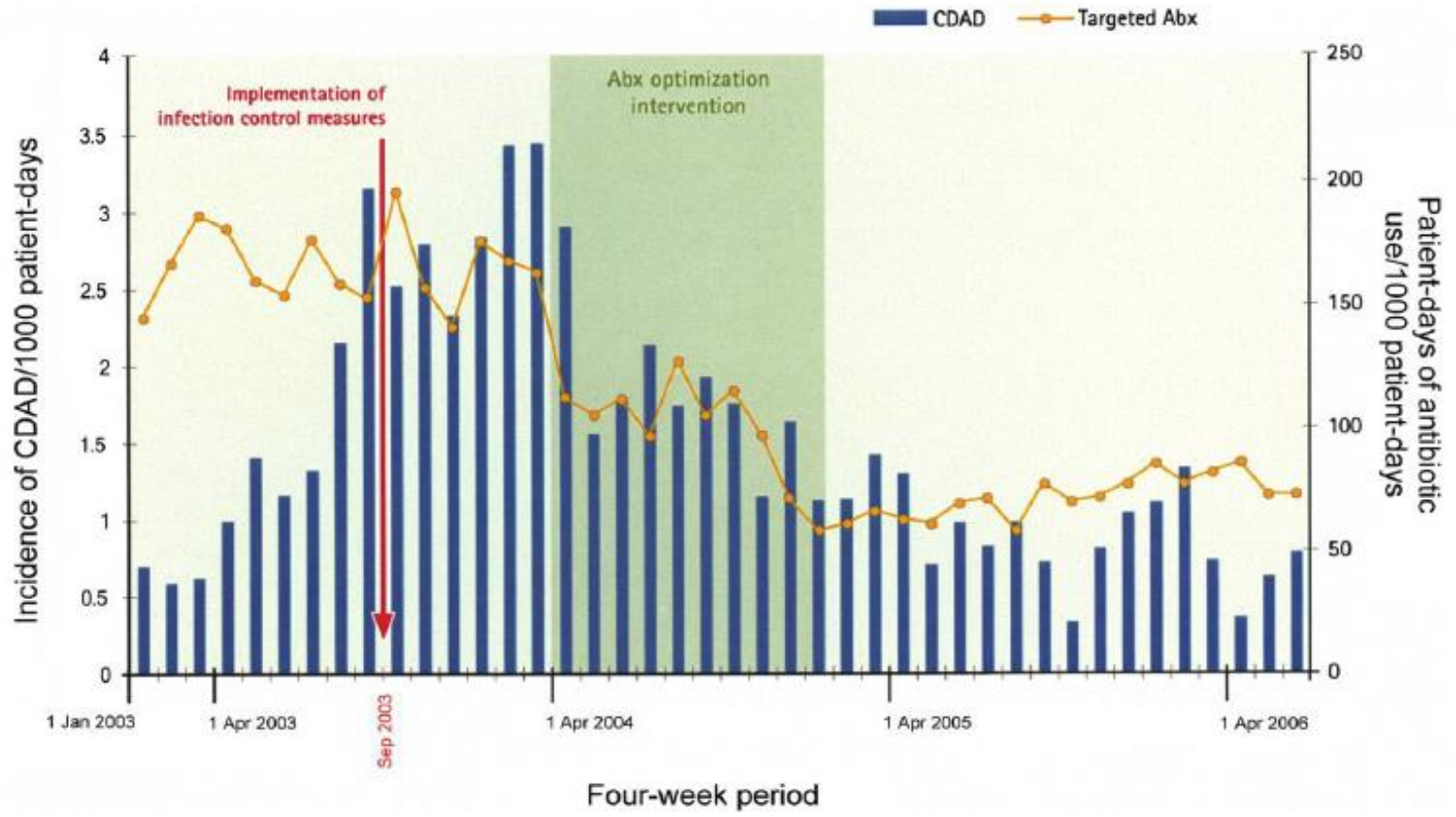
Vertical Tactics (Targeting *C. difficile*)

- **A**ccurate microbiology diagnostic testing
  - Toxin immunoassay negative result misses 30% of true positive cases
  - Confirm immunoassay negatives with molecular method
- **B**arrier and **C**ontact isolation precautions
  - Private room for LOS duration
  - PPE = gowns, gloves
    - Gloves reduce transmission
  - Soap and water hand hygiene preferred; hand sanitizer acceptable
    - Spores bind tightly to skin proteins

Horizontal Tactics (Targeting all organisms)

- **A**ntimicrobial Stewardship
- **C**ompulsive hand hygiene
  - No increase in CDI with use of alcohol based hand sanitizers or a decrease in CDI with soap and water
- **D**isinfection of the environment
  - Endemic rates: low level disinfectants are effective to reduce bioburden
  - Epidemic rates: Sporicidal agents (peroxide, bleach)
- **E**quipment Management
  - Dedicate equipment, where possible

Impact of a Reduction in the Use of High-Risk Antibiotics on the Course of an Epidemic of *Clostridium difficile*–Associated Disease Caused by the Hypervirulent NAP1/027 Strain



Cl Infect Dis 2007; 45:S112

CDI rates after an intervention to reduce high-risk anti-infectives

Year	Country	Stewardship method	Pre-intervention	Post-intervention	Reduction in CDI rates
1994	USA	Restictive use	15.8	1.9	88%
1997	UK	Restictive use	5.3	2.3	57%
1998	USA	Restictive use	11.5	3.3	71%
2003	UK	Restictive use	14.6	3.4	77%
2003	USA	Prospective audit and feedback	2.2	0.3	86%
2004	UK	Restictive use	46	22	52%
2004	USA	Restictive use	1.32	0.51	61%
2007	UK	Prospective audit and feedback	NR	NR	65%
2007	Canada	Restictive use	2.03	0.82	60%
2011	UK	Restictive use	2.22	0.45	80%
2012	Canada	Prospective audit and feedback	1.12	0.71	37%
2013	UK	Restictive use	2.398	1.2	50%

JAC 2014;69:1748-54

Stewardship and and C. *difficile* Reduction

- Antibiotic fluctuations can significantly impact CDI
  - *JAMA Intern Med. 2015; 175:626-33.*
  - Every 10% increase in unit level antibiotic exposure has been associated with a 2.1/per 10,000 increase in CDI
    - Association was the same regardless of recent antibiotic exposure and after adjustment for risk factors
- Successful clindamycin restriction significantly reduced CDI
  - *Ann Intern Med 1998; 128:989-995; Ann Intern Med 1994; 120:272-277*
- Reduction of broad-spectrum antibiotics prescribing (e.g. 3GC, FQ, pip/tz) significantly reduced CDI
  - *Infect Control Hosp Epidemiol 2012; 33:354-361.*
- Hospital-wide interventions targeting 3GC, FQ, and clindamycin significantly reduced CDI
  - *J Antimicrob Chemiother 2012; 67:2988-2996; Infect Control Hosp Epidemiol 2003; 24:699-706; J Antimicrob Chemother 2007; 59:990-995.*

Bringing It All Together

- Evidence based practice bundles to prevent CDI in hospitals:
  - Improving antimicrobial prescribing
  - Promptly identifying patients with CDI
  - High compliance with infection prevention tactics:
    - Placing patients with diarrhea in contact precautions
    - Gowns, gloves, hand hygiene
    - Use of dedicated equipment whenever possible
    - Disinfect non-dedicated equipment between patients.
  - Use effective disinfectants on the environment and equipment
  - ? Role of no touch technologies

Summary

- *C. difficile* associated with increased morbidity, mortality and costs
- Antibiotic Stewardship
  - Restrictive stewardship if possible
- PPI ‘Stewardship’
- Contact Precautions, Single Rooms, Dedicated Equipment
- Environmental Cleaning
- Hand Hygiene
- New approaches to modifying microbiome

Questions