

Clostridium difficile Infection: Current State of Prevention

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Objectives

- Review the impact, background and changing epidemiology of *C. difficile* and *C. difficile* Infection (CDI)
- Identify specific interventions designed to recognize cases of CDI early then facilitate preventive interventions
- Recognize limitations in our knowledge regarding effectiveness of interventions

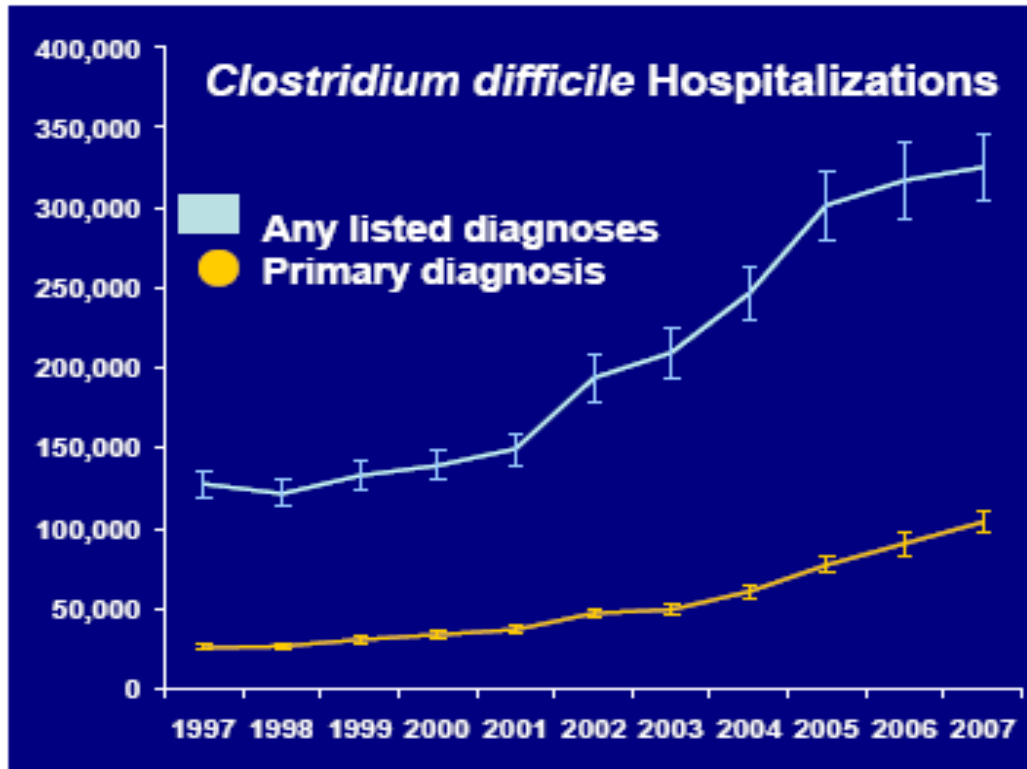
Disclosure

- Thanks to Drs. Cliff McDonald and Carolyn Gould with CDC for sharing the CDI Toolkit. Thanks to Dr. Julio Ramirez for the graphics
- Speakers bureau: CareFusion, Sanofi pasteur, MedImmune, Clorox

Scenario

- 76 year old woman admitted to hospital from a long term care facility with a diagnosis of pneumonia. After 4 days of antibiotic treatment, she develops diarrhea. Other symptoms include a temperature of 100.8F, WBC 15.5. Stool sent for C. difficile and was toxin+.

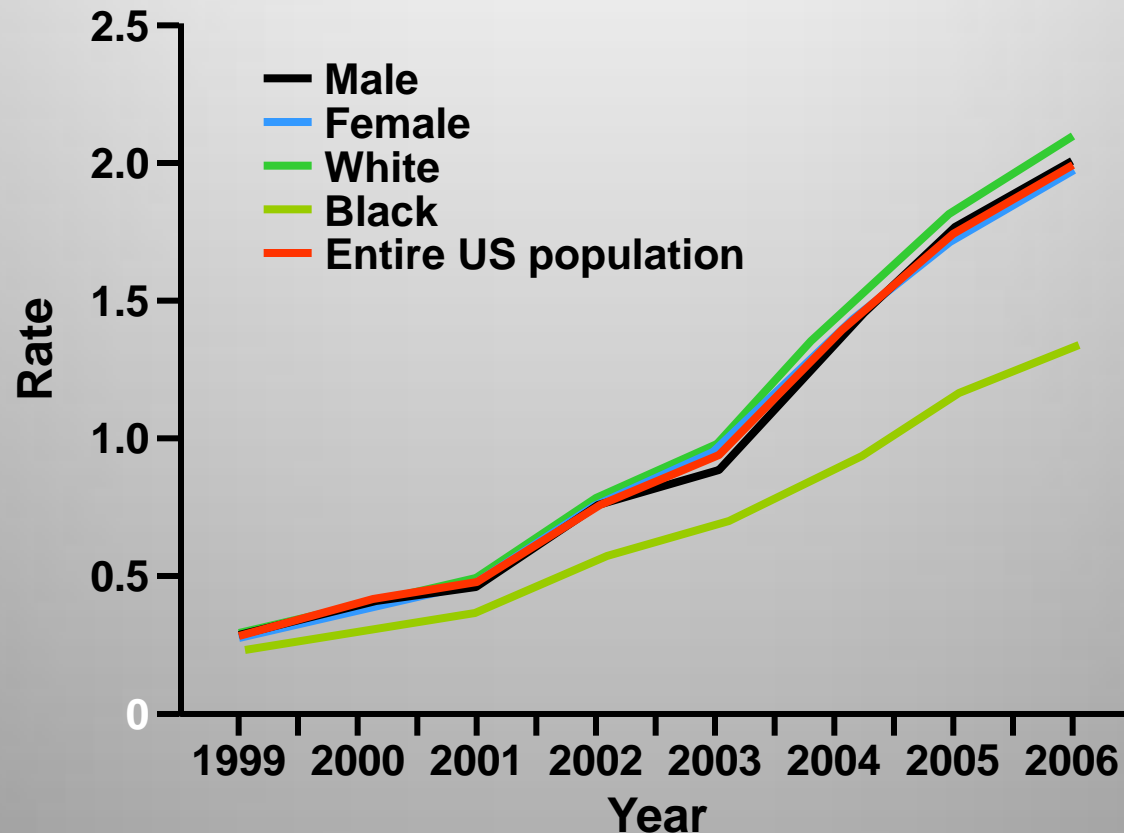
Impact of *C. difficile*



- CDC estimates that there are >300,000 cases of CDI annually with 15,000-30,000 attributable deaths.
- About half of the cases occur in long-term care facilities

Impact of CDI

Age-Adjusted Death Rate* for Enterocolitis Due to *C. difficile*, 1999–2006



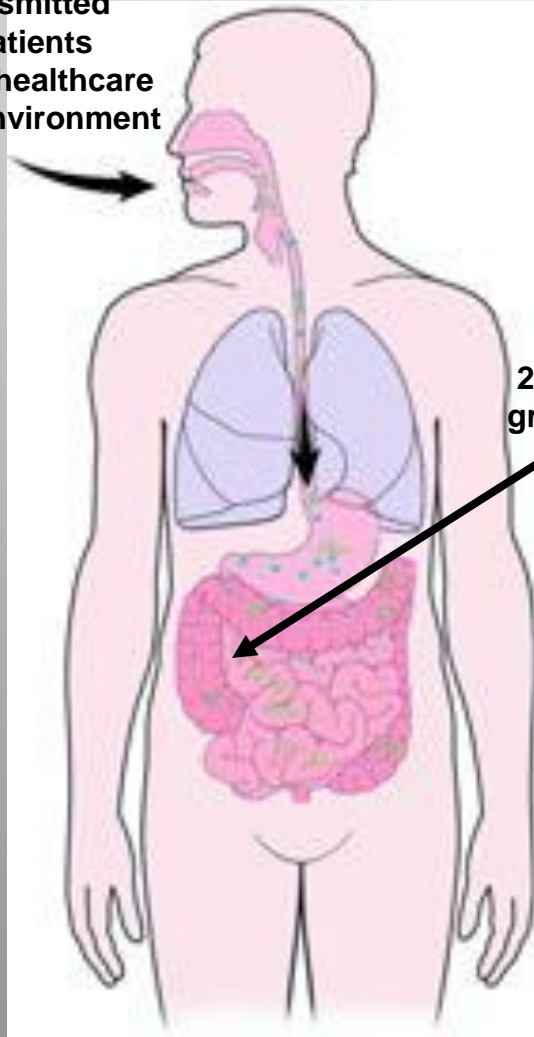
*Per 100,000 US standard population

Heron et al. Natl Vital Stat Rep 2009;57(14). Available at http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf



Pathogenesis of CDI

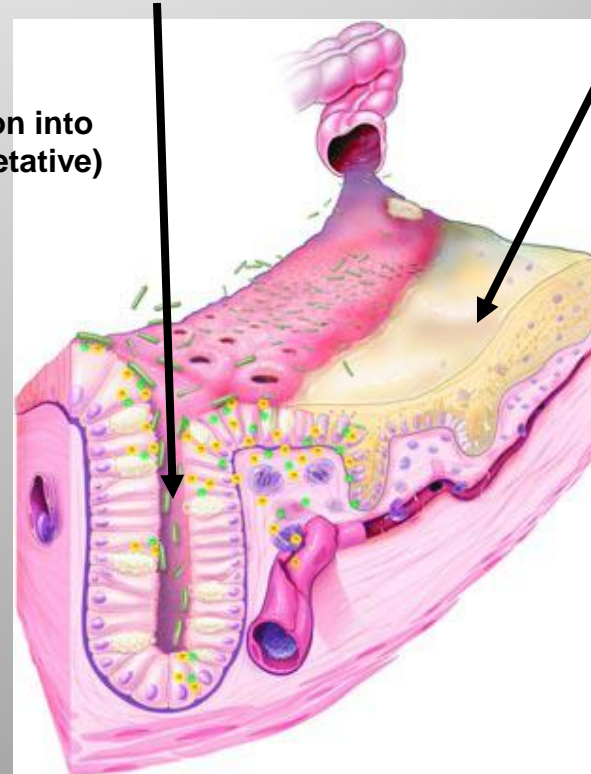
1. Ingestion of spores transmitted from other patients via the hands of healthcare personnel and environment



2. Germination into growing (vegetative) form

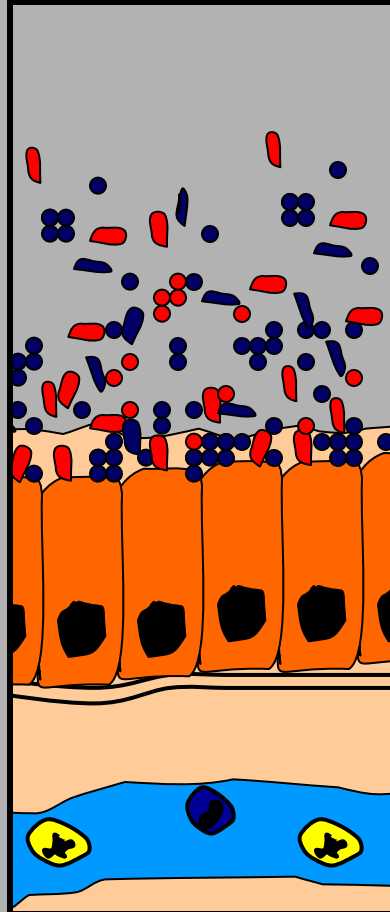
3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon

4. Toxin A & B Production leads to colon damage +/- pseudomembrane

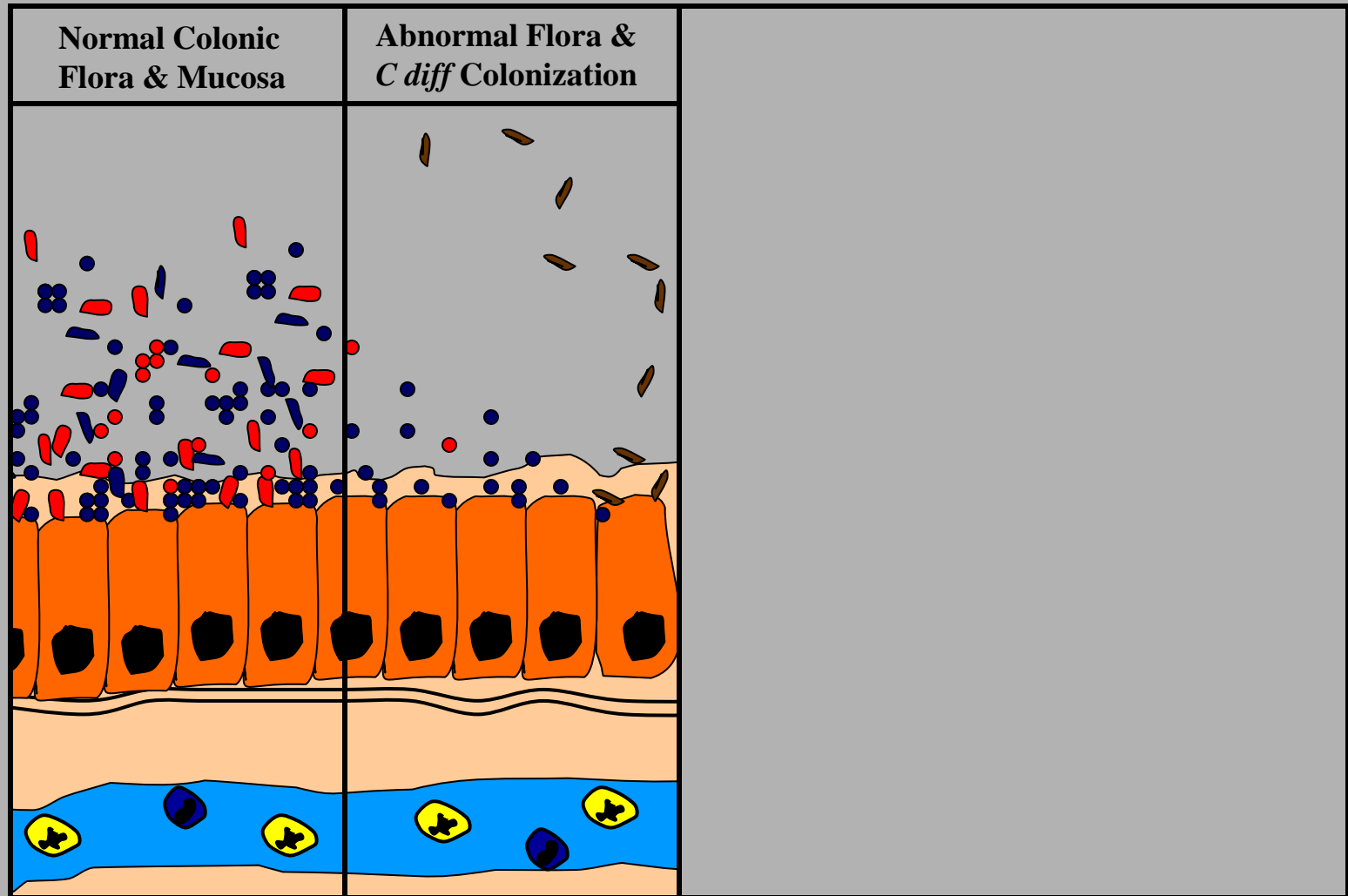


Pathogenesis of CDI

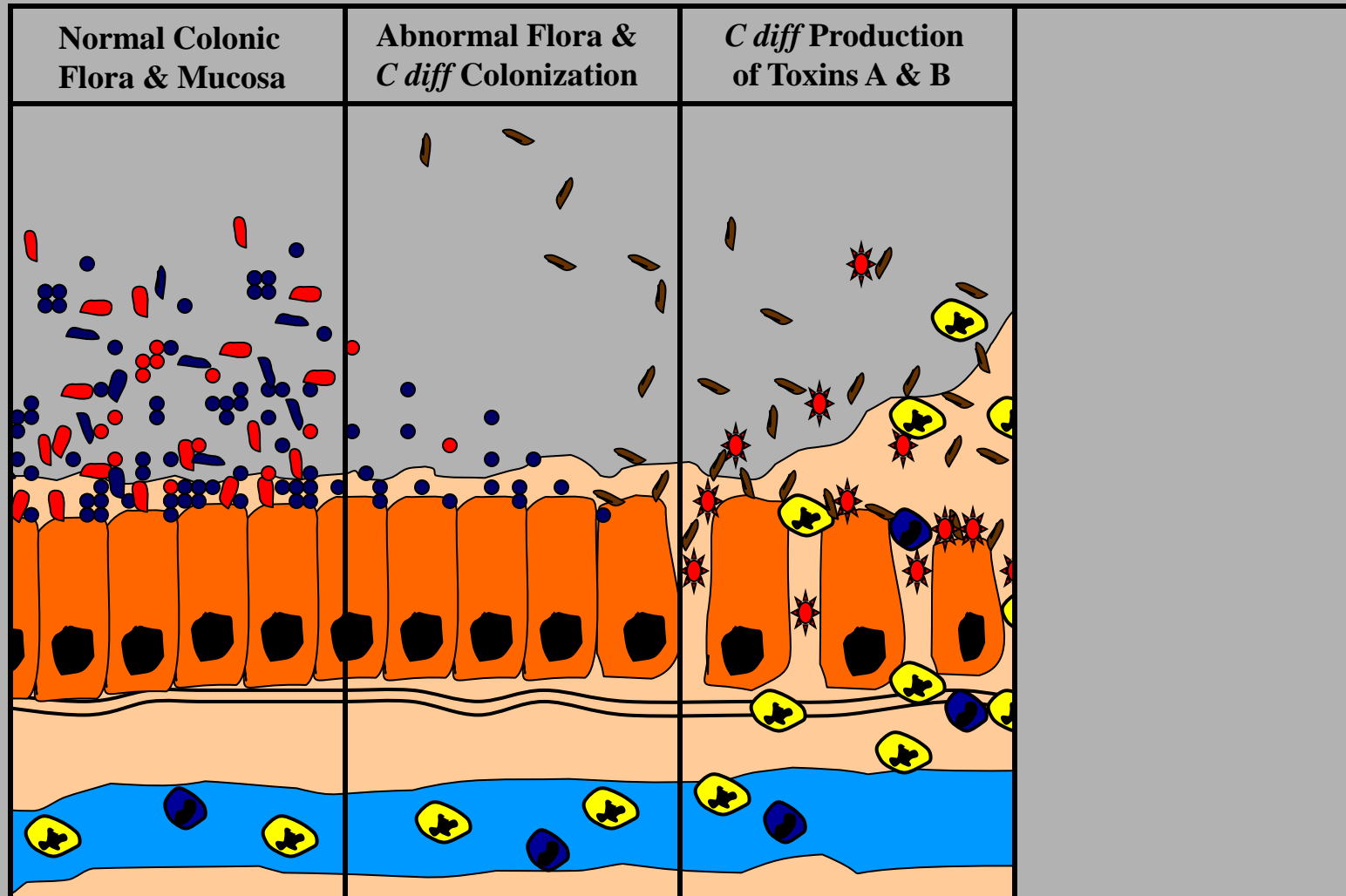
Normal Colonic
Flora & Mucosa



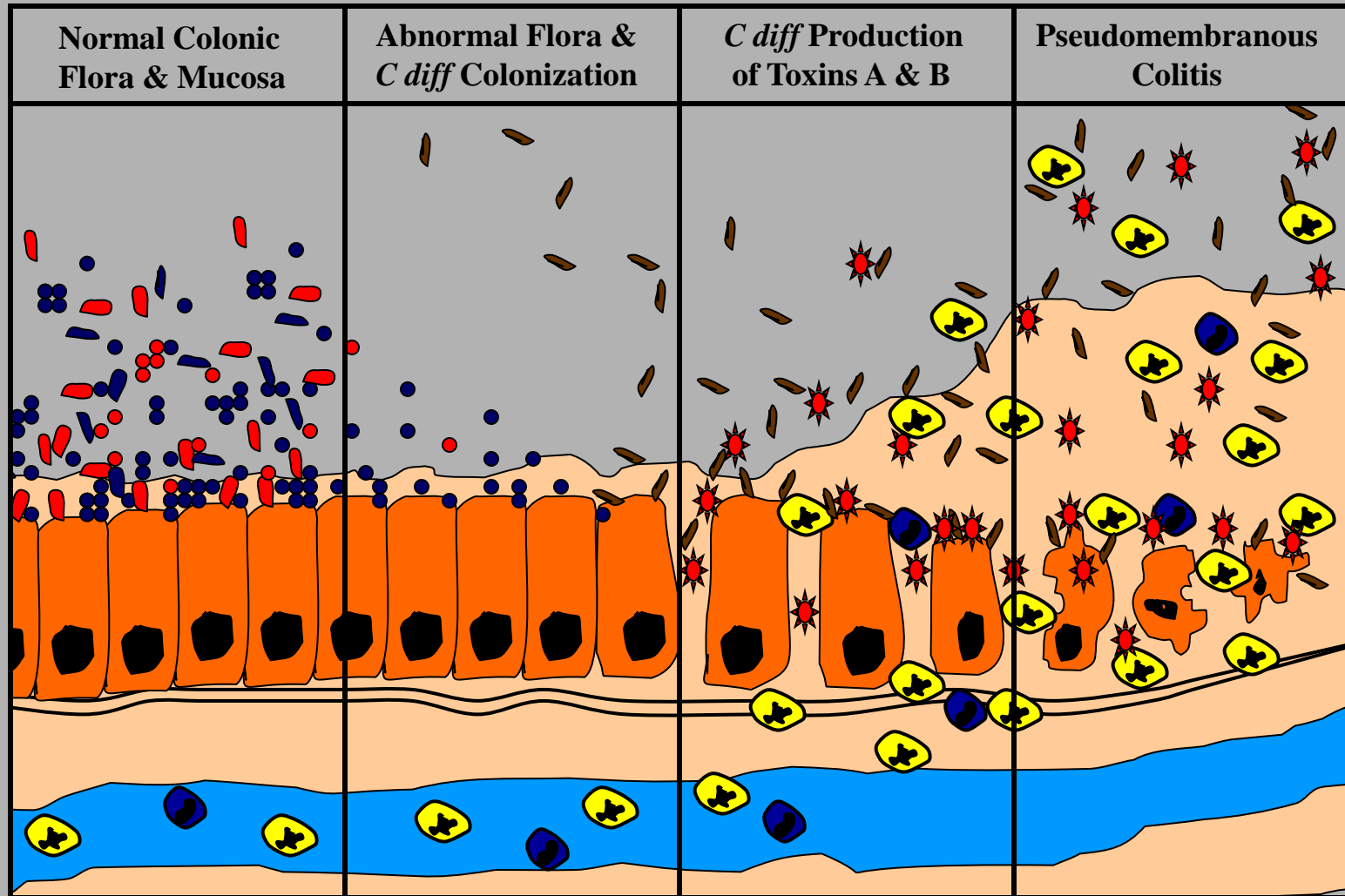
Pathogenesis of CDI



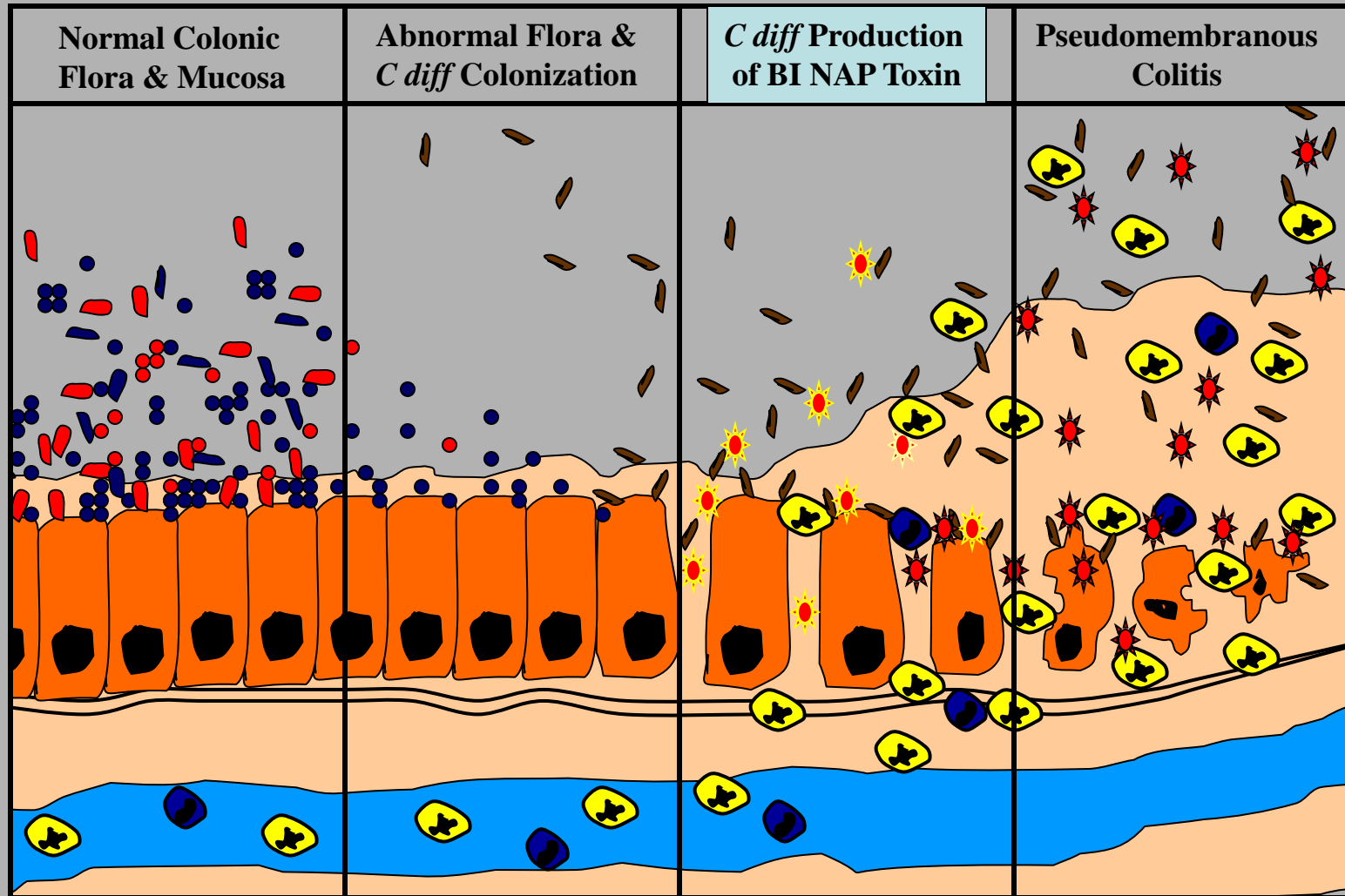
Pathogenesis of CDI



Pathogenesis of CDI



Pathogenesis of CDI



Current Epidemic Strain of *C. difficile*

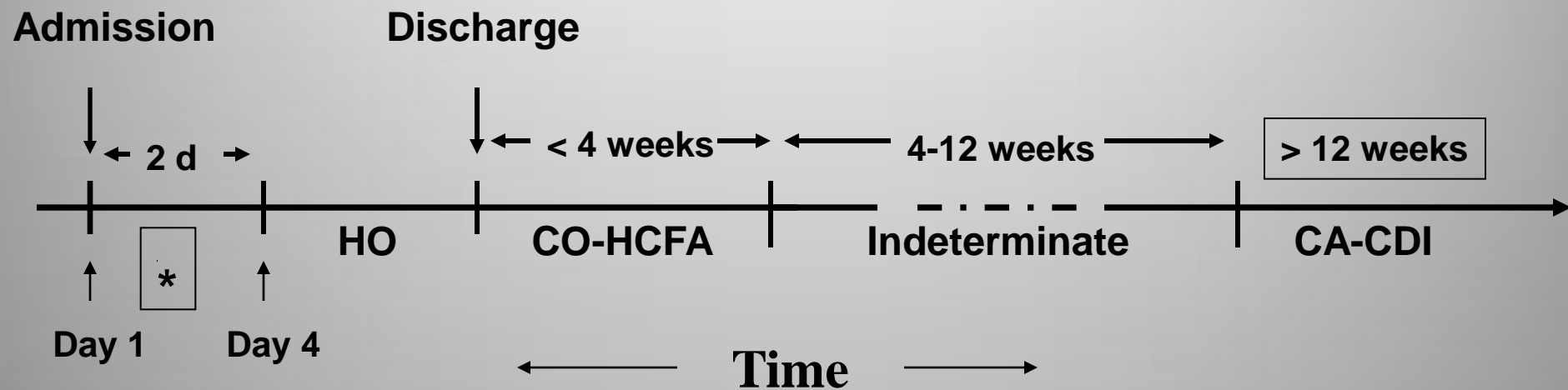
- BI/NAP1/027, toxinotype III
- Historically uncommon – epidemic since 2000
- More resistant to fluoroquinolones
 - Clindamycin and quinolones recognized as risk factors
 - Higher MICs compared to historic strains and current non-BI/NAP1 strains
- More virulent
 - Increased toxin A and B production
 - Increased sporulation

Risk Factors

- Antimicrobial exposure
- Acquisition of *C. difficile* organism
- Advanced age
- Underlying illness
- Immunosuppression
- Tube feeds
- Use of electronic thermometers
- ? Gastric acid suppression (PPI)

Surveillance:

Categorize Cases by location and time of onset



HO: Hospital (Healthcare)-Onset

CO-HCFA: Community-Onset, Healthcare Facility-Associated

CA: Community-Associated

* Depending upon whether patient was discharged within previous 4 weeks, CO-HCFA vs. CA

Prevention Strategies

- **Core Strategies**

- Should be first line prevention
- Some high levels of scientific evidence
- Demonstrated feasibility

- **Supplemental Strategies**

- May be implemented in response to epidemic or ongoing transmission
- Some scientific evidence
- Variable levels of feasibility

Prevention Strategies: Knowledge Gaps

- Lack of high quality studies
- Implementation of bundles may cloud recognition of what actually works
- What is the situational context in which prevention activities should be applied (e.g., does environmental disinfection prevent CDI transmission during outbreaks)?
- What are the unintended consequences that result from interventions?

Core Prevention Strategies

- Contact Precautions for duration of diarrhea
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system for immediate notification of positive test results
- Educate about CDI: HCP, housekeeping, administration, patients, families

http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_HCP.html

Dubberke et al. Infect Control Hosp Epidemiol 2008;29:S81-92.

Healthcare Personnel Education

- What is CDI
 - Diagnosis and treatment
 - Transmission to others
 - Isolation
 - Hand hygiene
 - Environmental cleaning
 - Discharge instructions
 - When to contact their clinician
-
- Excellent patient education handout in the APIC Elimination Guide

Patient/Family Education

- What is CDI
 - Diagnosis and treatment
 - Transmission to others
 - Isolation
 - Hand hygiene
 - Environmental cleaning
 - Discharge instructions
 - When to contact their clinician
-
- Excellent patient education handout in the APIC Elimination Guide

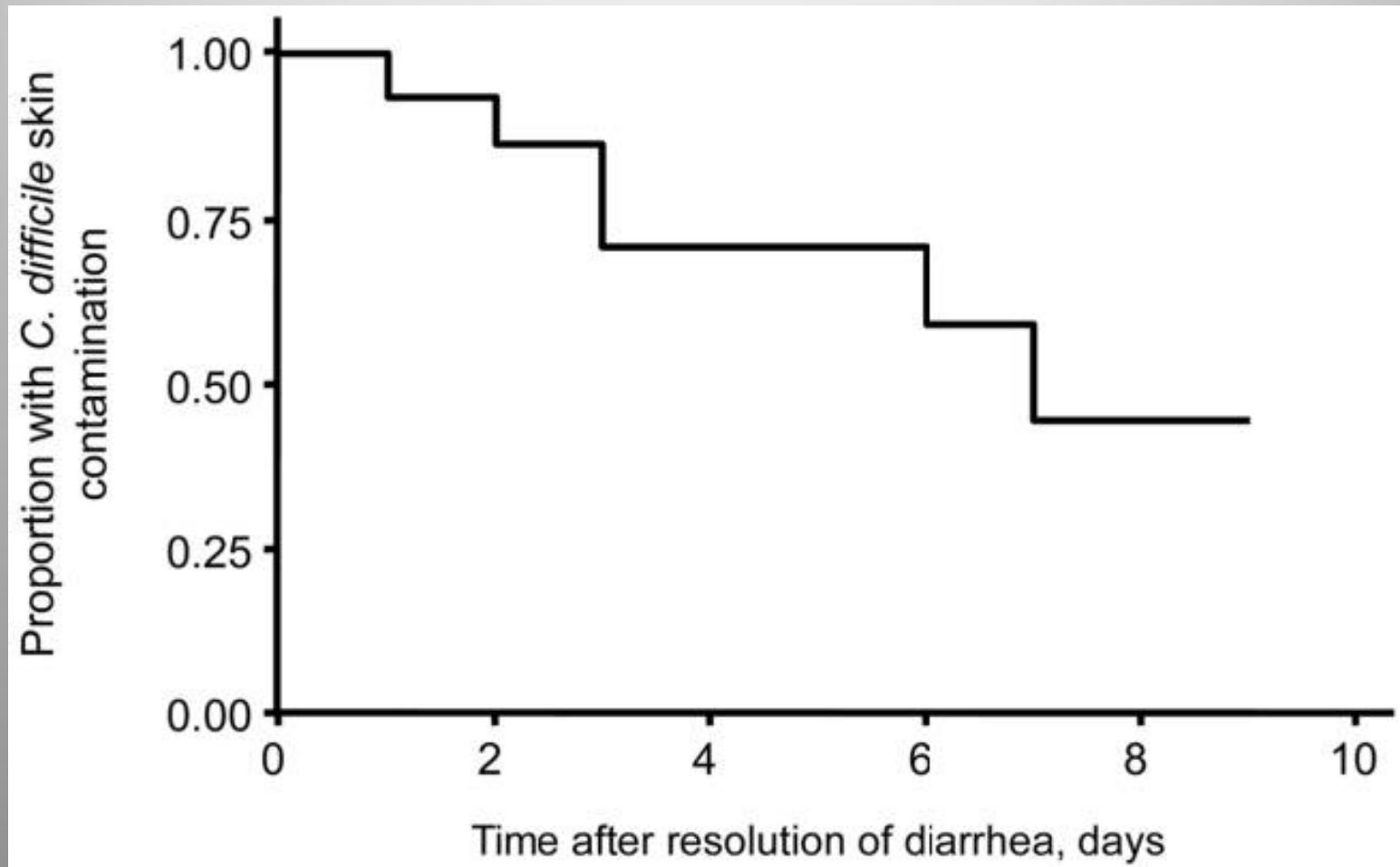
Supplemental Prevention Strategies

- Extend use of Contact Precautions beyond duration of diarrhea (e.g., 48 hours)*
- Presumptive isolation for symptomatic patients pending confirmation of CDI
- Evaluate and optimize testing for CDI
- Implement soap and water for hand hygiene before exiting room of a patient with CDI
- Implement universal glove use on units with high CDI rates*
- Use sodium hypochlorite (bleach) – containing agents for environmental cleaning
- Implement an antimicrobial stewardship program

* Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions

Supplemental Prevention Strategies:

Rationale for considering extending isolation beyond duration of diarrhea



Bobulsky et al. Clin Infect Dis 2008;46:447-50.

Supplemental Prevention Strategies:

Consider presumptive isolation for patients with ≥ 3 unformed stools within 24 hours

- Patients with CDI may contaminate environment and hands of healthcare personnel pending results of diagnostic testing
- CDI responsible for only ~30-40% of hospital-onset diarrhea
- However, CDI more likely among patients with ≥ 3 unformed (i.e. taking the shape of a container) stools within 24 hours
 - Information must be shared between shifts and HCP
 - Send specimen for testing and presumptively isolate patient pending results
 - Positive predictive value of testing will also be optimized if focused on patients with ≥ 3 unformed stools within 24 hours
 - Exception: patient with possible recurrent CDI (isolate and test following first unformed stool)

Supplemental Prevention Strategies:

Evaluate and optimize test-ordering practices and diagnostic methods

- Most laboratories have relied on Toxin A/B enzyme immunoassays
 - Low sensitivities (70-80%) lead to low negative predictive value
- Despite high specificity, poor test ordering practices (i.e. testing formed stool or repeat testing in negative patients) may lead to many false positives
- Consider more sensitive diagnostic methods but apply these more judiciously across the patient population
 - Employ a highly sensitive screen with confirmatory test or a PCR-based molecular assay
 - Restrict testing to unformed stool only
 - Focus testing on patients with ≥ 3 unformed stools within 24 hours
 - Require expert consultation for repeat testing within 5 days



Challenges in Diagnostic Methods

- EIA 70-80% sensitivity and 97% specificity (3% false +)
- Culture >90% sensitivity and 95-97% specificity
- PCR detects organism but not the toxin. Must combine results with clinical context
- Sensitivity- True positives
- Specificity- True negatives
 - 3% prevalence of disease and 3% false positive rate means that half of the positive tests will be false. With a 25% prevalence you will have a 8% false positive.

Challenges in Diagnostic Methods

- Must recognize when to test (not testing formed stool unless specific reasons to do so, defining what is meant by “diarrhea”, and determine how many samples to be tested during a diarrhea episode).
- If diagnostic methods change, it is important that it be known for both infection prevention and clinical decision-making purposes.
- Do not know if testing methods lead to improved patient outcomes

Supplemental Prevention Strategies: Hand Hygiene – Soap vs. Alcohol Hand Rub

- Alcohol not effective in eradicating *C. difficile* spores
- However, one hospital study found that from 2000-2003, despite increasing use of alcohol hand rub, there was no concomitant increase in CDI rates
- Discouraging alcohol hand rub may undermine overall hand hygiene program with untoward consequences for HAIs in general

Supplemental Prevention Strategies:

Hand Washing: Product Comparison

Product	Log10 Reduction
Tap Water	0.76
4% CHG antimicrobial hand wash	0.77
Non-antimicrobial hand wash	0.78
Non-antimicrobial body wash	0.86
0.3% triclosan antimicrobial hand wash	0.99
Heavy duty hand cleaner used in manufacturing environments* <small>* Only value that was statistically better than others</small>	1.21*

Conclusion: Spores may be difficult to eradicate even with hand washing.

Supplemental Prevention Strategies: Hand Hygiene Methods

- Since spores may be difficult to remove from hands even with hand washing, adherence to glove use, and Contact Precautions in general, should be emphasized for preventing *C. difficile* transmission via the hands of healthcare personnel
- Have hand hygiene practices make sense to HCP
- Must address hand hygiene needs and impact beyond CDI

Supplemental Prevention Strategies: Glove Use

Rationale for considering universal glove use (in addition to Contact Precautions for patients with known CDI) on units with high CDI rates

- Although the magnitude of their contribution is uncertain, asymptomatic carriers have a role in transmission
- There may be a role for universal glove use as a special approach to reducing transmission on units with longer lengths of stay and high endemic CDI rates
- General benefit in minimizing hand contamination

Supplemental Prevention Strategies: Environmental Cleaning

- Bleach can kill spores, whereas other standard disinfectants cannot
- Limited data suggest cleaning with bleach (1:10 dilution prepared fresh daily) reduces *C. difficile* transmission
- Two before-after intervention studies demonstrated benefit of bleach cleaning in units with high endemic CDI rates
- Therefore, bleach may be most effective in reducing burden where CDI is highly endemic

Mayfield et al. Clin Infect Dis 2000;31:995-1000.

Wilcox et al. J Hosp Infect 2003;54:109-14.



Supplemental Prevention Strategies: Environmental Cleaning

- Use of hypochlorite for disinfection B-II (moderate evidence to support recommendation, evidence from at least 1 well-designed clinical trial, multiple time-series or from dramatic results from uncontrolled experiment)
- in vitro exposure of epidemic *C. difficile* strains to subinhibitory concentrations of non-chlorine based cleaners significantly increased sporulation capacity
- Current evidence supports the use of chlorine-containing agents (with at least 1,000 ppm available chlorine) to address environmental contamination in areas associated with endemic or epidemic CDI.
- User acceptability, any health/safety concerns, and compatibility challenges must be assessed and addressed.

Supplemental Prevention Strategies: Environmental Cleaning

Assess adequacy of cleaning before changing to new cleaning product such as bleach

- Ensure that environmental cleaning is adequate and high-touch surfaces are not being overlooked
- Evaluate processes used in cleaning (clean to dirty, products support process)
- One study using a fluorescent environmental marker to assess cleaning showed:
 - only 47% of high-touch surfaces in 3 hospitals were cleaned
 - sustained improvement in cleaning of all objects, especially in previously poorly cleaned objects, following educational interventions with the environmental services staff
- If changing products, ensure staff can be successful with switching and sustaining

Supplemental Prevention Strategies:

Audit and feedback targeting broad-spectrum antibiotics

- Monitoring and feedback a critical element in antimicrobial stewardship programs
- A prospective, controlled interrupted time-series analysis in 3 acute medical wards for the elderly in the UK demonstrated the impact of antimicrobial management on reducing CDI.
 - Introduced a narrow-spectrum antibiotic policy
 - Reinforced using feedback
 - Associated with significant changes in targeted antibiotics and a significant reduction in CDI

Summary of Prevention Measures

Core Measures

- Contact Precautions for duration of illness
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system
- CDI surveillance
- Education

Supplemental Measures

- Prolonged duration of Contact Precautions*
- Presumptive isolation
- Evaluate and optimize testing
- Soap and water for HH upon exiting CDI room
- Universal glove use on units with high CDI rates*
- Bleach for environmental disinfection
- Antimicrobial stewardship program

* Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions

Process Measurement

- **Core Measures:**
 - Measure compliance with CDC/WHO recommendations for hand hygiene and Contact Precautions
 - Assess adherence to protocols and adequacy of environmental cleaning
- **Supplemental Measures:**
 - Intensify assessment of compliance with process measures
 - Track use of antibiotics associated with CDI in a facility

C. difficile Treatment

- Metronidazole 500 mg po TID
- Vancomycin 125 mg po QID
- Vancomycin > 125 mg po QID
- Vancomycin enema
- Probiotics (e.g., a yeast *Saccharomyces boulardii*, in conjunction with antibiotics)
- Fecal transplant
- New drugs (e.g., Fidaxomicin, a new class of narrow-spectrum macrocyclic antibiotics)



Laboratory-identified MDRO or CDAD Event

OMB No. 0920-0
Exp. Date: 03-31-2

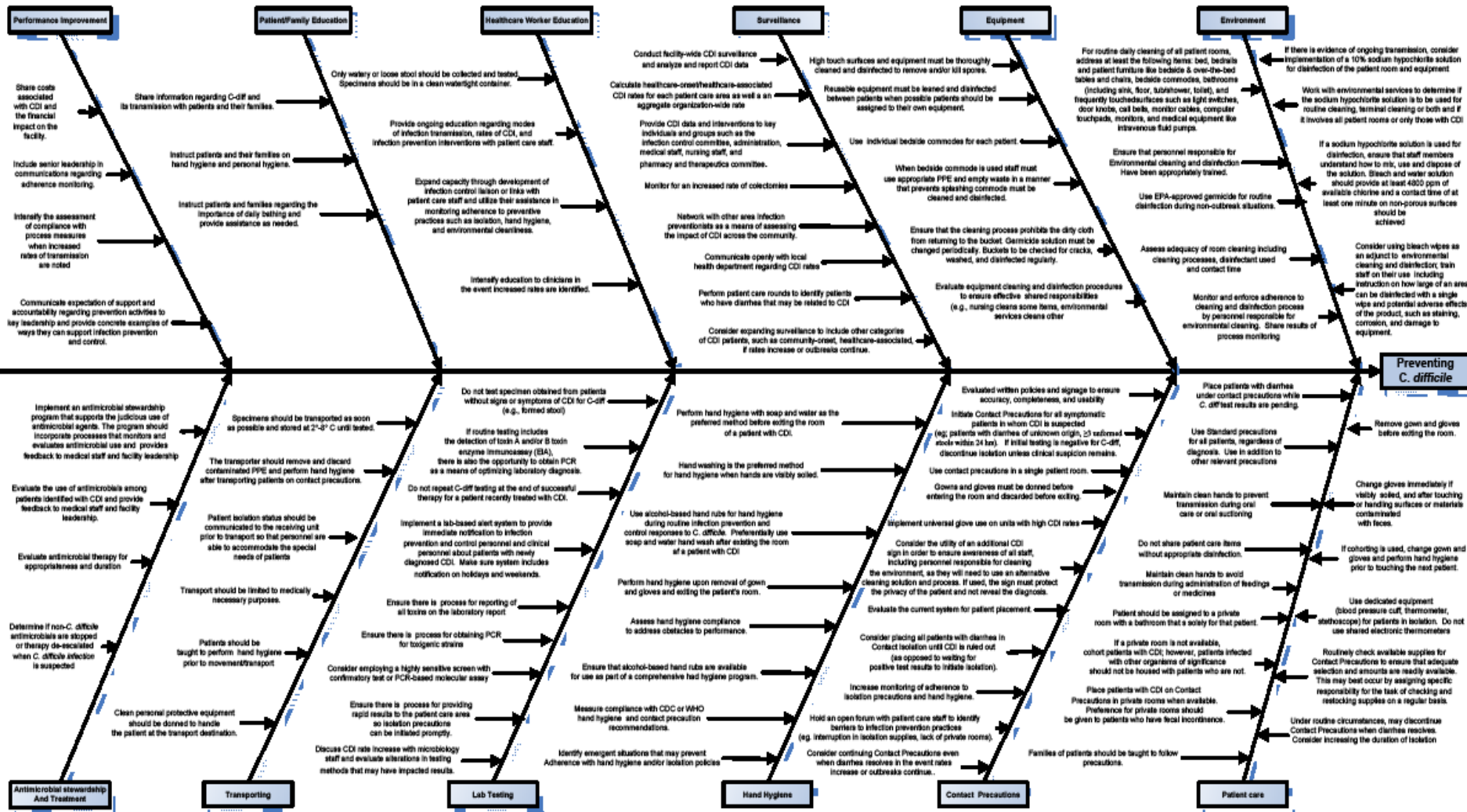
*required for saving	
Facility ID:	Event #:
*Patient ID:	Social Security #:
Secondary ID:	

Patient Name, Last:	First:	Middle:
*Gender: M F	*Date of Birth:	
Ethnicity (Specify):	Race (Specify):	

Event Details

*Event Type: LabID	*Date Specimen Collected:	
*Specific Organism Type: (Check one) <input type="checkbox"/> MRSA <input type="checkbox"/> MSSA <input type="checkbox"/> VRE <input type="checkbox"/> MDR-Klebsiella <input type="checkbox"/> MDR-Acinetobacter <input type="checkbox"/> C. difficile		
*Outpatient: Yes No	*Specimen Source:	
*Date Admitted	*Location:	*Date Admitted

Preventing Transmission of *Clostridium difficile* in Healthcare Settings



Primary Sources:

- APIC. Guide to the Elimination of *Clostridium difficile* in Healthcare Settings, 2008.
- Dubberke E, Gerding DN, Classen D, Arfas K, Podgorny K, et al. Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals. *ICHE*, October 2008, Vol. 29, Supp 1, S81-S92.
- CDC. *Clostridium difficile* (CDI) Infections Toolkit. Activity C. ELC Prevention Collaborative 2009

SHEA-IDSA GUIDELINE

**Clinical Practice Guidelines for *Clostridium difficile*
Infection in Adults: 2010 Update by the Society for Healthcare
Epidemiology of America (SHEA) and the Infectious Diseases
Society of America (IDSA)**

**Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD;
L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD**

Since publication of the Society for Healthcare Epidemiology of America position paper on *Clostridium difficile* infection in 1995, significant changes have occurred in the epidemiology and treatment of this infection. *C. difficile* remains the most important cause of healthcare-associated diarrhea and is increasingly important as a community pathogen. A more virulent strain of *C. difficile* has been identified and has been responsible for more-severe cases of disease worldwide. Data reporting the decreased effectiveness of metronidazole in the treatment of severe disease have been published. Despite the increasing quantity of data available, areas of controversy still exist. This guideline updates recommendations regarding epidemiology, diagnosis, treatment, and infection control and environmental management.

Infect Control Hosp Epidemiol 2010; 31(5):431-455

APIC Elimination Guide

Carrico et al. Guide to the Elimination of *Clostridium difficile* in Healthcare Settings. 2008. Available at www.apic.org

Practical approaches that address CDI in healthcare settings. Epidemiology, diagnosis, surveillance, prevention, frequently asked questions.

Additional Resources

SHEA/IDSA Compendium of Recommendations

CDI Checklist Example

S81 INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY OCTOBER 2008, VOL. 29, SUPPLEMENT 1

SUPPLEMENT ARTICLE: SHEA/IDSA PRACTICE RECOMMENDATION

Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals

Erik R. Dubberke, MD; Dale N. Gerding, MD; David Classen, MD, MS; Kathleen M. Arias, MS, CIC;
 Kelly Podgorny, RN, MS, CPHQ; Deverick J. Anderson, MD, MPH; Helen Burstin, MD; David P. Calfee, MD, MS;
 Susan E. Coffin, MD, MPH; Victoria Fraser, MD; Frances A. Griffin, RRT, MPA; Peter Gross, MD; Keith S. Kaye, MD;
 Michael Klompas, MD; Evelyn Lo, MD; Jonas Marschall, MD; Leonard A. Mermel, DO, ScM; Lindsay Nicolle, MD;
 David A. Pegues, MD; Trish M. Perl, MD; Sanjay Saint, MD; Cassandra D. Salgado, MD, MS;
 Robert A. Weinstein, MD; Robert Wise, MD; Deborah S. Yokoe, MD, MPH

Dubberke et al. Infect Control Hosp Epidemiol 2008;29:S81-92.
 Abbett SK et al. Infect Control Hosp Epidemiol 2009;30:1062-9.

Clostridium difficile Infection (CDI) Checklist

Hospital interventions to decrease the incidence and mortality of healthcare-associated *C. difficile* infections

Prevention Checklist

• When an MD, PA, NP, or RN suspects a patient has CDI:

Physician, Physician Assistant, or Nurse Practitioner:

- Initiate *Contact Precautions Plus*
- Order stool *C. difficile* toxin testing
- Discontinue non-essential antimicrobials
- Discontinue all anti-peristaltic medications

Registered Nurse:

- Obtain stool sample for *C. difficile* toxin test
- Place patient in single-patient room
- Place *Contact Precautions Plus* sign on patient's door
- Ensure that gloves and gowns are easily accessible from patient's room
- Place dedicated stethoscope in patient's room
- Remind staff to wash hands with soap and water following patient contact

Microbiology Laboratory Staff Person:

- Call relevant patient floor with positive *C. difficile* toxin test result
- Provide daily list of positive test results for Infection Control

Infection Control Practitioner:

- Check microbiology results daily for positive *C. difficile* toxin results
- Call relevant floor to confirm that patient with positive *C. difficile* toxin results is in a single-patient room and that the *Contact Precautions Plus* sign is on the patient's door
- Flag the patient's *C. difficile* status in the hospital's clinical information system or in the patient's paper chart
- Alert housekeeping that the patient is on *Contact Precautions Plus*

Environmental Services Staff Person:

- Prior to discharge cleaning, check for *Contact Precautions Plus* sign on the patient's door
- If *Contact Precautions Plus* sign is on the door, clean the room with a bleach-based cleaning agent
- Confirm for supervisor that bleach-based cleaning agent was used for discharge cleaning for every patient on *Contact Precautions Plus*

Treatment Checklist

• When an MD, PA, or NP diagnoses mild CDI: All of the following criteria are present: diarrhea (<6 BM/day), no fever, WBC<15,000, no peritoneal signs, and no evidence of sepsis

Physician, Physician Assistant, or Nurse Practitioner:

- Initiate oral metronidazole at dose 500mg every 8 hours
- If no clinical improvement by 48-72 hours after diagnosis, treat patient as moderate CDI
- Continue therapy for at least 14 days total and at least 10 days after symptoms have abated

• When an MD, PA, or NP diagnoses moderate CDI:

At least one of the following criteria is present: diarrhea (6-12 BM/day), fever >38.5°C, WBC >25,000, hemodynamic instability, marked & continuous abdominal bleeding

Physician, Physician Assistant, or Nurse Practitioner:

- Initiate oral vancomycin at dose 250mg every 6 hours
- If no clinical improvement by 48 hours, add IV metronidazole at dose 500mg every 8 hours
- Consider obtaining infectious disease consultation
- Consider obtaining abdominal CT scan
- Continue therapy for at least 14 days total and at least 10 days after symptoms have abated

• When an MD, PA, or NP diagnoses severe CDI: At

least one of the following criteria is present: diarrhea (>12 BM/day), fever >38.5°C, WBC >25,000, hemodynamic instability, marked & continuous abdominal pain, ileus, absence of bowel sounds, evidence of sepsis, or intensive care unit level of care required

Physician, Physician Assistant, or Nurse Practitioner:

- Obtain immediate infectious disease consultation
- Obtain immediate general surgery consultation
- Obtain abdominal CT scan
- Initiate oral vancomycin at dose 250mg every 6 hours together with IV metronidazole at dose 500mg every 8 hours
- Following consultation with general surgery regarding its use, consider rectal vancomycin
- Ask general surgery service to assess the need for colectomy

Abbreviations: MD=medical doctor, PA=physician assistant, NP=nurse practitioner, RN=registered nurse, BM=bowel movement, WBC=white blood cell count, CT=computed tomography, IV=intravenous

FIGURE 1. *Clostridium difficile* infection checklist at Brigham and Women's Hospital.

References

- Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; [Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America \(SHEA\) and the Infectious Diseases Society of America \(IDSA\)](#). Infect Control Hosp Epidemiol. 2010 May;31(5):431-55.
- Dubberke ER, Butler AM, Reske KA, et al. attributable outcomes of endemic *Clostridium difficile*-associated disease in nonsurgical patients. Emerg Infect Dis 2008;14:1031-8.
- Dubberke ER, Reske KA, Olssen MA, et al. Short- and long term attributable costs of *Clostridium difficile*-associated disease in nonsurgical inpatients. Clin Infect Dis 2008;46:497-504.
- Edmonds S, Kasper D, Zepka C, et al. *Clostridium difficile* and hand hygiene: spore removal effectiveness of handwash products. Presented at: SHEA 2009; Abstract 43.

References

- Elixhauser, A. (AHRQ), and Jhung, MA. (Centers for Disease Control and Prevention). *Clostridium Difficile-Associated Disease in U.S. Hospitals, 1993–2005*. HCUP Statistical Brief #50. April 2008. Agency for Healthcare Research and Quality, Rockville, MD. <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf>
- Fowler S, Webber A, Cooper BS, et al. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. *J Antimicrob Chemother* 2007;59:990-5.
- Heron MP, Hoyert DL, Murphy SL, et al. *Natl Vital Stat Rep* 2009;57(14). US Dept of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf
- Johnson S, Gerding DN, Olson MM, et al. Prospective, controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. *Am J Med* 1990;88:137-40.

References

- Mayfield JL, Leet T, Miller J, et al. Environmental control to reduce transmission of *Clostridium difficile*. *Clin Infect Dis* 2000;31:995–1000.
- McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene–variant strain of *Clostridium difficile*. *N Engl J Med*. 2005;353:2433-41.
- McDonald LC, Coignard B, Dubberke E, et al. Ad Hoc CDAD Surveillance Working Group. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol* 2007; 28:140-5.
- Oughton MT, Loo VG, Dendukuri N, et al. Hand hygiene with soap and water is superior to alcohol rum and antiseptic wipes for removal of *Clostridium difficile*. *Infect Control Hosp Epidemiol* 2009; 30:939-44.

References

- Peterson LR, Robicsek A. Does my patient have *Clostridium difficile* infection? Ann Intern Med 2009;15:176-9
- Riggs MM, Sethi AK, Zabarsky TF, et al. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. Clin Infect Dis 2007; 45:992–8.
- SHEA/IDSA Compendium of Recommendations. Infect Control Hosp Epidemiol 2008;29:S81–S92.
<http://www.journals.uchicago.edu/doi/full/10.1086/591065>
- Stabler RA, Dawson LF, Phua LT, et al. Comparative analysis of BI/NAP1/027 hypervirulent strains reveals novel toxin B-encoding gene (tcdB) sequences. J Med Micro. 2008;57:771–5.

References

- Sunenshine RH, McDonald LC. *Clostridium difficile*-associated disease: new challenges from an established pathogen. *Cleve Clin J Med*. 2006;73:187-97.
- Warny M, Pepin J, Fang A, Killgore G, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet*. 2005;366:1079-84.
- Wilcox MF, Fawley WN, Wigglesworth N, et al. Comparison of the effect of detergent versus hypochlorite cleaning on environmental contamination and incidence of *Clostridium difficile* infection. *J Hosp Infect* 2003;54:109-14.